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JMA Professional Medical Liability Insurance Program

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Yuhei MIYASAKA

Executive Member, Board of Trustees, Japan Medical Association

Key words: Adverse events; Medical malpractice; Malpractice litigation; Risk management; Safety measures

Introduction

Inadequate measures taken following the collapse of "bubble economy" deteriorated the Japanese economic basis and created enormous financial deficits in the beginning years of the 21st century. On the other hand, the Japanese society suffers from a sense of obstruction as it is faced with a myriad of problems ranging from fewer numbers of children and ageing society to those in education, environment conservation, and international coordination.

While the Japanese government is currently promoting "structural reform without sanctuary" to solve these problems by introducing the mechanism of market economy and focusing on efficiency, our concern is that the reform might lead to the decline of our social security system that we are so proud of. The government should not value speed above quality, but should proceed with caution so as to achieve the consensus of the society.

Structural reform is needed also in the field of medical care. The basis for reform lies in information disclosure and the manner with which we make the disclosure.

I would like to discuss the relationship between information disclosure and adverse events occurring in medical practice.

Adverse events are unfortunate for both the patient and the physician, and every effort should be taken to prevent it. However, there are regrettably a large number of adverse events in medical practice today. For those physicians who take the utmost care in securing the patient safety and dispensing quality medical care, this is quite infuriating and most deplorable. This situation erodes people's confidence in medical care and amplifies their anxiety.

Many things are unforeseeable in the world of natural sciences and still more are yet to be elucidated. As medicine is practiced by applying highly developed sciences, there may occur incidents that could not have been anticipated. However, recent adverse events appear to occur as a result of most rudimentary error rather than that of using highly advanced scientific technology. Those of us engaged in medical care cannot help feeling anxiety.

If an adverse event did occur and if a party was proven responsible for the accident, that party should pay for consequences. For this

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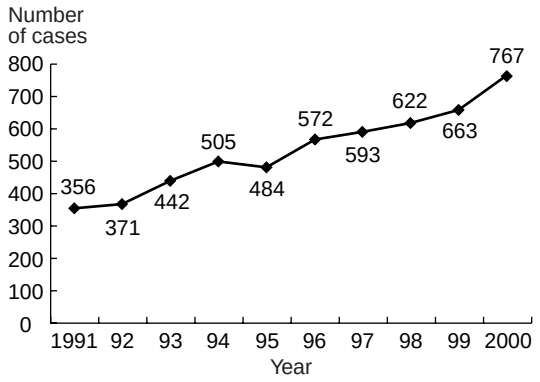

Fig. 1 Changes in the number of new medical malpractice suits accepted at the courts of the first instance in Japan (Source: Supreme Court of Japan)

purpose, relevant parties should take out the medical malpractice liability insurance.

Current Status of Medical Malpractice Litigation in Japan

According to the Japanese Supreme Court, the number of new malpractice suits filed at the courts of the first instance in Japan was in the order of 300 a year in 1992, 400 to 500 in 1993 onward, and radically increased to 767 in 2000. This is an increase of 215% in 10 years (Fig. 1).

This radical increase reflects the serious degree of damage to the confidential doctor-patient relationship, and may serve as an indicator of people's distrust in physicians.

Naturally, the medical side is not necessarily responsible for all the accidents over which malpractice suits have been brought. The court rendered unfavorable decisions for the medical sides in 37% of the cases during the past decade. This may appear that the medical side won a majority of cases, but one must not overlook that settlement was reached before the decision in 49% of all cases. A considerable number of cases were concluded by thus recognizing the fault of the medical side.

The author acutely feels that the medical profession should face this situation seriously and structure a system under which the patient may receive treatment with a sense of security.

Risk Management in Medical Care

I would like to consider the risk management in medical care.

1. Concept of risk management

The concept and practice of risk management developed in manufacturing and transportation industries for "self-defense of companies."

This aims at snipping buds of risk before factors that inhibit perpetual development of business surface, and maximally preventing disadvantage such as the lowered corporate image, labor management problems, and economical losses, to thereby secure healthy corporate management.

For instance, risks and their countermeasures include (1) minimizing damage to facilities caused by natural disasters such as earthquakes, typhoons, fires, and explosions, (2) taking thorough accident prevention measures in aviation, automobile, and transportation where the passenger safety is of the utmost importance, (3) hedging risks in foreign exchange and asset management, and (4) others. Risk management focuses on precisely identifying the mechanism under which a risk occurs, and structuring and implementing the system to avoid risks.

2. Risk management in medical care

Physicians offer daily medical care with respect for human life and appreciation of patient's confidence in them. Since enormous risks are involved in their work and a great damage may be inflicted once an accident occurs, introduction of the risk management was considered necessary.

It was in the middle of 1970s that risk management techniques were introduced to the medical field in the United States to address the so-called "medical malpractice crisis." As is well known, it was the time when laws related to "the patient right" were legislated and attorneys for the patient played active parts. Against such a background, medical malpractice litiga-

tions rapidly increased. The number of cases lost by the medical side jumped and the amount of damages soared causing many physicians and medical institutions to go bankrupt.

Insurance companies could not bear increases in the cases lost and the amount of damages, and were forced to back out from this type of insurance or to raise the insurance premium radically.

Under the situation such as the above, the risk management was introduced so that medical institutions might maintain the quality of medical care and bear out the malpractice litigations. Initially, the risk management was a measure taken to solidify the financial basis and to secure the fund for damage payment, but the emphasis gradually shifted to prevention of medical injury themselves. Therefore, the risk management may be described as 1) the safety measure in medical care by preventing medical injury themselves, and 2) the means to pay damage to the patient in the event of medical injury.

Safety Measures in Medical Care

Japan Medical Association has taken the following measures for safety in medical care.

In order to offer safe medical care, JMA has taken various measures and presented proposals including establishing the Committee for Safety Measures in Medical Care in 1997. They consisted, among others, of (1) proposing "Risk management in medical care," (2) proposing "Research on medical safety and needs for training personnel," (3) establishing "the Department for Securing Patient Safety," and (4) offering "Training courses for personnel in charge of medical safety." JMA is determined to pursue safety in medical care as its most important challenge.

Safety measures in medical care should be based on a mature confidential relationship between the physician and the patient. The means to achieve such a relationship are discussed below.

1. Training in medical technology

First of all, physicians and medical care personnel should constantly pursue training in medical technology. Progress and development in medical care and medicine are remarkable today. Physicians should therefore pursue lifelong studies constantly, should not lag behind the progress in medicine, should acquire expertise knowledge for diagnosis and treatment, and should train themselves in applying the knowledge to clinical medicine. Not only the physicians but also those persons engaged in nursing, etc. should daily endeavor to improve their knowledge and continue studies in order to offer quality medical care.

The administration system of the medical facility as a whole should not be ignored. Constant reviews are needed of the systems of responsibility taking by physicians and of work assignment by nurses. Hardware such as buildings, facilities, machinery, and apparatuses should naturally be kept in optimum conditions by appropriate maintenance.

Court decisions in medical malpractice proceedings are based on evaluation of "the medical standard" prevailing at the time. The physician should always keep abreast with the current medical standards and continue research in order to respond to expectations of the patient.

2. Good communication

The next point concerns communication with the patient. In the past, treatment tended to be uniform as diseases were usually acute diseases, mainly infectious diseases. Therefore, the patient tended to entrust everything to the doctor, and the doctor used to take the paternalistic attitude. Medical care was offered and received based on tacit understandings without verbal information or explanation. Today, however, diseases are mainly chronic, and the means employed to treat chronic diseases are diverse. Often a disease is to be controlled rather than cured, and the patient should live with the disease. Thus, the patient often

consults the physician about the ways of coexisting with the disease. Thus, the doctor-patient communication becomes most important in order to have the patient understand that he/she should take the initiative to overcome the disease.

If the physician or nurse were to treat the patient perfunctorily without appreciating the latter's suffering or without giving adequate information about the disease, problems are bound to occur, and offering of complete medical care is impossible. The physician should be aware of his/her own role, and know that medical care begins by first establishing the confidential doctor-patient relationship based on good communication.

According to a research, there are four reasons why the patient brings medical malpractice suit against the physician.

One concerns communication. The patient complains that "information offered by the doctor was insufficient," "the doctor did not appreciate his/her feelings and ignored them," "the doctor and nurse were not courteous to the patient in attitude or language," "they lacked understanding or care of the patient's suffering," and "they did not apologize for the damage suffered by me." The second reason is that "they should try to prevent recurrence of accident," the third reason "they should pay for damage," and the fourth reason "they should be punished severely."

The paper reported that an overwhelming number of litigations were started because of inadequate communication. Communication is thus critical, and patients usually do want to improve communication.

3. Informed consent

The third point concerns informed consent. The physician has the duty to inform and also the right to use discretion in treating the patient. On the other hand, the patient has the right to learn the truth and that of self-determination. Maintaining a balance between the two is the difficulty in clinical medicine.

It is important that the physician gives sufficient information in easy-to-understand words about symptoms, diagnosis, treatment regimen, prognosis, etc., so that the patient understands and accepts the proposed treatment before starting the treatment. This way, therapeutic effects are said to improve.

With advance and progress in medical care, the patient sometimes has excessive expectations. The patient tends to think that all diseases are curable by the physician. If the outcome is not what he/she had expected, the patient incurs distrust toward the physician, and this may lead to a dispute. Sufficient explanation about prognosis should be attempted, understood, and accepted. Adequate history taking regarding past drug allergy episodes is also important, and the patient should be explained fully that unforeseeable or unavoidable accidents could occur in medical care.

For instance, the discovery of antibiotics, a major research achievement of the last century, has drastically improved therapeutic effects for infectious diseases, but the patient should be made to understand that there might be unforeseeable side effects.

At any rate, medical care based on informed consent given as a result of smooth communication between the patient and the doctor is essential, and the conventional paternalism may cause problems.

JMA Professional Medical Liability Insurance Program

1. Creation and purposes

The second point concerning the risk management is how to address the adverse event if it does occur. In order to compensate the patient adequately, sufficient financial resources or funds for damage payment should be secured. The best answer to this is to take out the medical liability insurance.

Japan Medical Association created the current JMA Professional Medical Liability Insurance in 1973 as a system for adequately address-

ing disputes over adverse event that involve its Class A Members.

The insurance system is participated by all of its Class A Members under the spirit of mutual aid, and the Investigation Committee, Japan Medical Association, local medical associations coordinate together in dealing with examinations by the Medical Liability Review Board, a fair third party organ, and in resolving disputes with cooperation from the members.

Since its start, this Insurance Program has greatly contributed to fair and proper settlement of medical disputes, and has always advocated the ideal ways of resolving disputes.

Despite the recent increase in the number of malpractice litigations in Japan, "medical malpractice crisis" faced by our American colleagues has not emerged in Japan. I am confident that the system has greatly contributed to development of Japan's national medical care.

2. Outline of JMA Professional Medical Liability Insurance Program

JMA Professional Medical Liability Insurance is outlined below.

(1) JMA's Category A Members (A1 or A2) or physicians who subscribe to JMA by paying the membership fee can be insured.

The insurance contract is entered between JMA and a non-life insurance company (such as the Tokio Marine & Fire Insurance [the managing company], the Yasuda Fire & Marine Insurance, Nihon Koa Fire & Marine Insurance, Mitsui Marine & Fire Insurance, and Sumitomo Marine & Fire Insurance (the last two companies having merged as of October 1, 2001 is now called Mitsui Sumitomo Marine & Fire Insurance), and the JMA members do not need to take any procedure for insurance.

By payment of the prescribed membership fees, JMA Category A Members automatically become insured.

If a person becomes a Category A Member during the year, he/she will qualify as the insured party under the JMA Professional Medical Liability Insurance, but will disqualify if he/she loses the Category A Membership.

(2) If the demand for damage exceeds ¥1,000,000 for physical disorder attributable to a medical act, the accident is covered by the insurance. Accidents attributable to the ownership, use, or administration of building/equipment of medical facilities are not covered.

(3) Insurance money paid by JMA Professional Medical Liability Insurance covers the damage paid to the patient and the legal fees. The damage paid by the insurance (maximum amount) is ¥100 million per year per insured party (with the legal fees paid separately).

(4) The exemption amount (or the amount to be borne by the insured) is ¥1,000,000 per medical act. In other words, only the portion of damage in excess of ¥1,000,000 will be paid by the JMA Professional Medical Liability Insurance. There is no exemption for the legal fees.

(5) When a medical accident occurs and the patient demands damage payment, details from the time the accident occurred leading to the dispute should be reported to the local medical association to which the physician belongs. The latter Association will guide the member based on the instruction of the local medical associations. Pending on the investigation result, the local medical associations will decide whether or not the incident will be entrusted to the JMA Professional Medical Liability Insurance processing.

(6) The matter entrusted to JMA will be investigated and discussed by "the Investigation Committee" working under the JMA Professional Medical Liability Insurance, and presented to the "Medical Liability Review Board," a fair and neutral review organization. Based on the review result, JMA management policy is notified to the local medical associations. According to the policy, the member in question will try to settle the dispute under the guidance of the local medical associations to which he/she belongs.

(7) JMA Professional Medical Liability Insurance has a different scheme from those of physicians' medical liability insurances taken

out by clinics and hospitals.

JMA Professional Medical Liability Insurance insures only its Category A Members, and the insurance money will be paid for damage attributable to the Category A Member as an individual. If the review finds a party other than JMA Category A Member responsible for an accident, the portion attributable to such other party shall not be covered by the insurance, and will be deducted from the insurance money.

JMA Professional Medical Liability Insurance is managed in a restricted way because the insurance premiums are paid from the membership fees of the Category A Members. Thus, it is different from general medical liability insurances under which the right to seek remedy from the responsible party for the accident is waived in advance.

JMA Professional Medical Liability Insurance with Special Clause

JMA Professional Medical Liability Insurance with Special Clauses (the Special Clause Insurance), which was created in 2001, is explained below.

1. Creation and purposes

As discussed above, the current JMA Professional Medical Liability Insurance basically insures its members against liability for their medical act. Therefore, if a Category A Member who is the founder or administrator of a hospital or a clinic employs a physician who is not a Category A member (non-A member), and the physician causes a medical accident and the Category A Member is demanded to pay damage as the responsible administrator, the insurance does not extend to the liability of the non-A member. The same applies to an entity such as a medical corporation.

Therefore, the insurance money is paid by deducting the amount for damage that is attributable to a non-A party member. This is called "the payment deduction." The amount thus not covered by the insurance was often borne by the Category A Member as the founder or administrator of the clinic or hospital.

The recent trend is that the amount of insurance payment exceeds the maximum liability.

In view of such a situation, "JMA Special Clause Insurance" that the Category A Members may optionally take out was created as of September 1, 2001 to cover the Category A Member who is also an administrator or to enable the member to pay high damages.

2. Outline of the Special Clause Insurance

(Fig. 2)

The Special Clause Insurance covers the amount in excess of the maximum coverage of the current JMA Professional Medical Liability Insurance, and the Category A Members may choose to take out this insurance.

Applications for the insurance are accepted by the local medical association to which the Category A member belongs, and the Japan Medical Association enters the contract as the insurer with a non-life insurance company. Similar to the current JMA Professional Medical Liability Insurance, the contract is entered directly between JMA and the insurance company without an agent.

The premium is collected by the due date upon instruction of the local medical association. If the insurance premium is not collected by the due date, the insurance becomes invalid retrospectively.

The system of dispute settlement for medical accident is the same as the current JMA Professional Medical Liability Insurance.

(1) **The insurer**

Only the Category A Member is qualified to become the insurer. Non-A Members are not qualified. Those Category A Members whose fees are exempted by JMA may pay the prescribed fees and become the insured party.

(2) **Taking out the insurance**

This is a voluntary insurance for the Category A Members.

(3) **The insured**

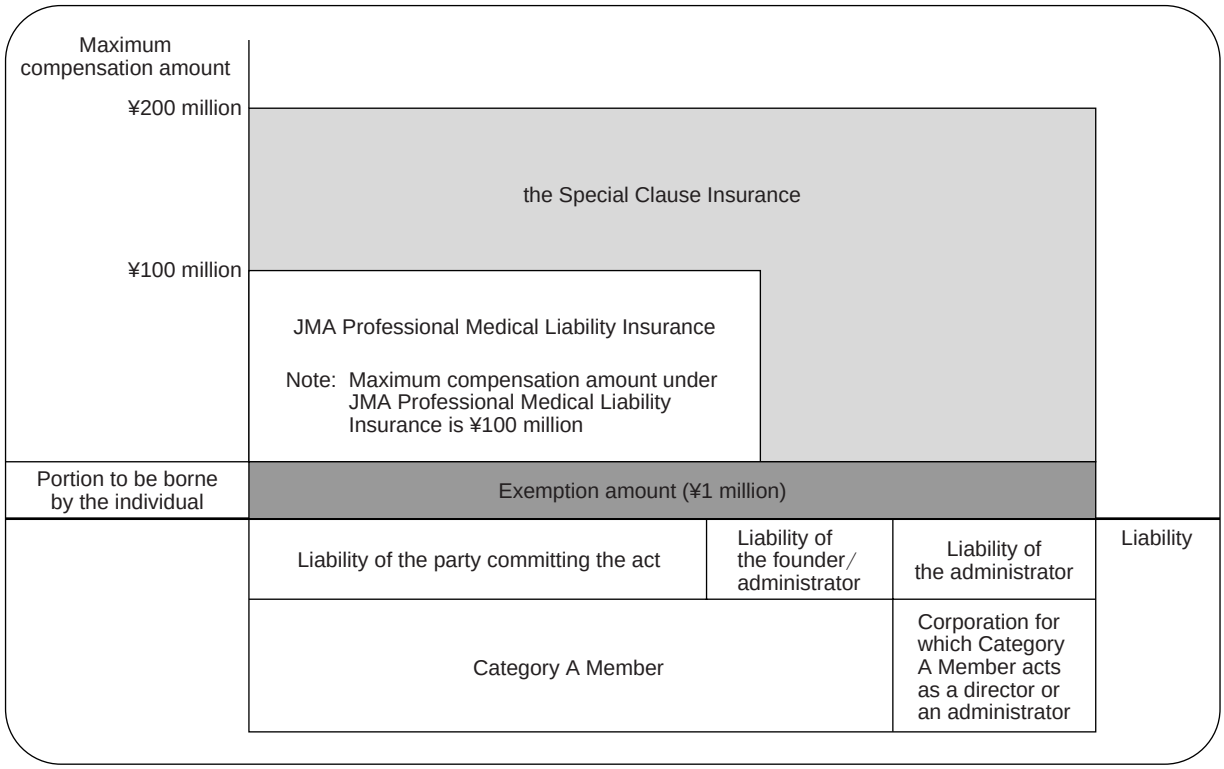

Fig. 2 JMA Professional Medical Liability Insurance and its relation to "Special Clause Insurance"

The Category A Member (the registered member) and the corporation managing a medical facility for which the Category A Member serves as the director or administrator (the registered corporations) are insured; such medical facilities include (1) clinics, (2) hospitals established by individuals, and (3) hospitals with 99 or less beds established by corporations. The following two points should be noted.

* A non-A member physician working in such a medical facility is not insured. Therefore, if a non-A member physician is demanded payment of damage by a patient, this Special Clause Insurance is not applicable.
* Medical facilities that are managed by the government, social insurance schemes, companies or public medical facilities (including clinics and hospitals in both instances) are not applicable.

(4) **Payment of insurance money**

Under the "Special Clause Insurance," the Category A Member who is the insured party is paid the full amount of the insurance money for the damage for which a non-A member is specifically liable.

Provided, however, if the non-A member is insured by the general medical liability insurance, payment is shared by the JMA Professional Medical Liability Insurance and JMA Special Clause Insurance. In other words, if the non-A member is insured by other medical liability insurance such as by his/her affiliated specialized medical society, the portion that is attributable to the non-A member is paid by the said insurance.

(5) **Insurance money and maximum compensation amount**

The insurance money consists of the payment for damage and the legal fees. The total maximum compensation per year is ¥200 million per accident (of the same medical act) and

the total amount for the entire insurance period (per year) is ¥600 million. The maximum compensation amount is applied to the sum of damage of the registered member and the registered corporation.

(6) **Exemption Amount**

The amount exempted per medical act is ¥1 million per accident. Provided, however, this amount is not applicable when the insurance money is paid from JMA Professional Medical Liability Insurance.

(7) **Insurance period and procedure**

Since the Special Clause Insurance is the special policy condition of JMA Professional Medical Liability Insurance, and their insurance periods coincide or it is one year from July 1 every year, the insurance can be taken out once a year, as a rule.

Provided, however, the exceptional measure was taken for the year 2001; ten months from September 1, 2001 to July 1, 2002, and six months from January 1, 2002 to July 1, 2002.

The Category A Members wishing to take out the insurance should submit the application at least two and a half months prior to the start date to the local medical association.

When a hospital established by a corporation and having 99 or less beds wishes to switch to this insurance from the general medical liability insurance, the period may be shorter and monthly installments may be made, i.e. from the first day of the month in which the former insurance expires until July 1. In this case, the hospital should apply to the local medical association at least two and a half months prior to the start of insurance.

(8) **Insurance premium and payment method**

The premiums are classified for clinics, the Category A Members, and hospitals, and collected through the local medical associations.

(9) **Exercise of the right to claim for damage**

Any exercise of the right to claim for damage will be examined by the Medical Liability Review Board. The current JMA Professional Medical Liability Insurance reserves the right to claim for damage and the present Special Clause Insurance does the same.

The Special Clause Insurance shall pay the insurance money in full to the Category A Member for the portion attributable to the non-A member if the Category A Member is so demanded. Provided, however, a non-A member may be asked to pay for the damage after the Category A Member is paid the insurance money in full.

Exercise of this right to claim for damage shall be subject to examination by the Medical Liability Review Board.

(10) **Accident at medical facilities**

Both the Special Clause Insurance and the current JMA Professional Medical Liability Insurance do not cover accidents attributable to the ownership, use, or administration of medical facilities. We recommend taking out "facility damage insurance" aside from insurances discussed in this paper. Special care should be taken by facilities such as hospitals where patients are admitted.

(11) **Others**

The insurance for the Category A Member will be automatically renewed in the ensuing years unless the conditions change.

The Special Clause Insurance was outlined and discussed. The Special Clause Insurance is managed along with the JMA Professional Medical Liability Insurance in order to deal with disputes involving serious medical accidents, and will therefore function to improve the financial basis.

For details of these two insurances, reference should be made to the commentary attached to the JMA Journal dated June 1, 2001 (Vol. 125, No. 11).

Conclusion

The society's interests in the matters of medical care, particularly those of medical accidents, are mounting. As people's awareness of their rights changes and medical sciences advance further, disputes involving medical accidents are expected to become more com-

plex and increase in quality and quantity.

Medical care givers and patients alike desire quality medical care and the environment where patients can receive secure and safe care. Physicians should, therefore, strive to promote and implement measures for securing the patient safety.

JMA Professional Medical Liability Insurance and the Special Clause Insurance are characterized by uniquely excellent features and sound management. However, these systems need to be optimally balanced. The best measure to prevent the medical liability insurances from becoming bankrupt is to offer safe medical care and secure the patient safety.

To secure the patient safety and to manage the JMA Professional Medical Liability Insurance as the hedge against accidents, JMA is resolved to continue its serious endeavors. We welcome proposals and suggestions from our members and thank for their continued support.

Current Progress in Breast Cancer Treatment: A Consideration of QOL

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Shigemitsu TAKASHIMA

Director, National Shikoku Cancer Center Hospital

Abstract: The quality of life (QOL) is a subjective concept consisting of four elements, i.e., physical, functional, mental/psychological, and social aspects. Although the methods for determining and analyzing QOL have not yet been established, QOL is now recognized as an important factor in evaluating cancer treatment, together with the survival rate and tumor size reduction. Radical mastectomy, a technique developed at the end of 19th century, enabled cure of breast cancer. This procedure involves en bloc resection of the primary focus and regional lymph nodes. Just over a century thereafter, various extended or limited operations were attempted with the aim of improving treatment results and decreasing surgical damage. Clinical studies comparing these techniques demonstrated no significant difference between survival rates after mastectomy and breast-conserving surgery combined with radiotherapy. Although both techniques are widely used as standard breast cancer treatments, the results of QOL assessment are not necessarily consistent. Breast-conserving therapy achieves patient satisfaction in terms of cosmetic outcome because the breast is preserved. However, fear of local recurrence and anxiety about radiotherapy offset this advantage. The patient should be provided with accurate information, as well as mental and physical support, when choosing a method for breast cancer treatment.

Key words: Breast cancer; Surgery; QOL; Breast-conserving therapy

Introduction

Cancer treatment options have been increasing along with a rising number of cases with early stage cancers resulting from advances in diagnostic techniques, elucidation of the biological properties of cancer through molecular biologic studies, and the development of new surgical, radiological or pharmacological therapies. Optimal treatment selection must be based on evidence obtained from clinical trials using the survival rate or the rate of tumor reduction as end points. However, it is becoming increasingly difficult to identify differences

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in terms of conventional end points alone.

Quality of life (QOL) is the patient's subjective viewpoint composed of multi-dimensional concepts. Since there are no established methods for determining or analyzing these factors, QOL has occasionally been criticized for lacking a scientific base. However, a number of clinical trials using QOL as an end point have been carried out, and QOL now appears to be a key concept in the field of cancer treatment, in addition to informed consent.

The present report outlines breast cancer treatment, focusing particularly on surgical therapy, which seems to have the greatest influence on QOL.

Cancer Treatment and QOL

The origin of the QOL concept can be found in Karnovsky's research, which was conducted at the end of the 1940s. In Western countries, this issue has been discussed chiefly from the viewpoint of protecting human rights. From about 1980, analyses of QOL in cancer treatment began to be published. In 1985, the US Food and Drug Administration approved the addition of QOL as an end point in clinical trials of new anticancer drugs.

In Japan, QOL has been studied mainly in relation to chronic diseases such as hypertension, diabetes, asthma, and rheumatism. Studies of QOL in cancer treatment have lagged far behind those in Western countries. The reasons for this delay include the absence of consensus about telling patients that they have cancer and informed consent and disregard by clinicians who considered the data on QOL to merely be the results of questionnaire surveys, and thus not amenable to scientific analysis.

In recent years, it has become generally understood that the use of questionnaires whose reliability and validity have been statistically demonstrated provides objective and reproducible results. Under these circumstances, studies on QOL have made rapid progress, and clinical trials using QOL as an end point have been undertaken.

QOL varies according to the type of disease, culture, and the patient's race, nationality, gender, age, educational level, and income. Nearly complete consensus has been reached that QOL is a multi-dimensional concept consisting of common physical, functional, mental/psychological, and social aspects as well as items specific to the disease. Such specific items include, for instance, body image and sexual function in the setting of breast cancer treatment. In patients with cancer in the terminal stage, spiritual factors such as a feeling of happiness may be added.

Breast Cancer Surgery and QOL

1. History of breast cancer surgery

The oldest record of surgical treatment for cancer is breast cancer surgery during the ancient Greek era. In the 17th century, knowledge of topographic anatomy and tumors was expanded through human cadaver dissection, and surgery for cancer of the body surface including breast cancer began to be performed sporadically. In 1805, a Japanese doctor, Seishu Hanaoka, performed breast cancer surgery under general anesthesia for the first time in the world.

In 1894, Halsted developed radical mastectomy, paying attention to topographic anatomy and the mode of progression. This technique achieved cure of breast cancer in some cases. Radical mastectomy involves en bloc resection of the breast and axillary lymph nodes with the pectoralis major muscle and pectoralis minor muscle, assuming that the primary focus will metastasize to the regional axillary lymph nodes through lymph vessels and then cause hematogenous distant metastasis. This en bloc resection of the primary focus and regional lymph nodes contributed to the establishment of standard surgery for other organs, serving as the basic technique for curing cancer.

Thereafter, extended radical mastectomy

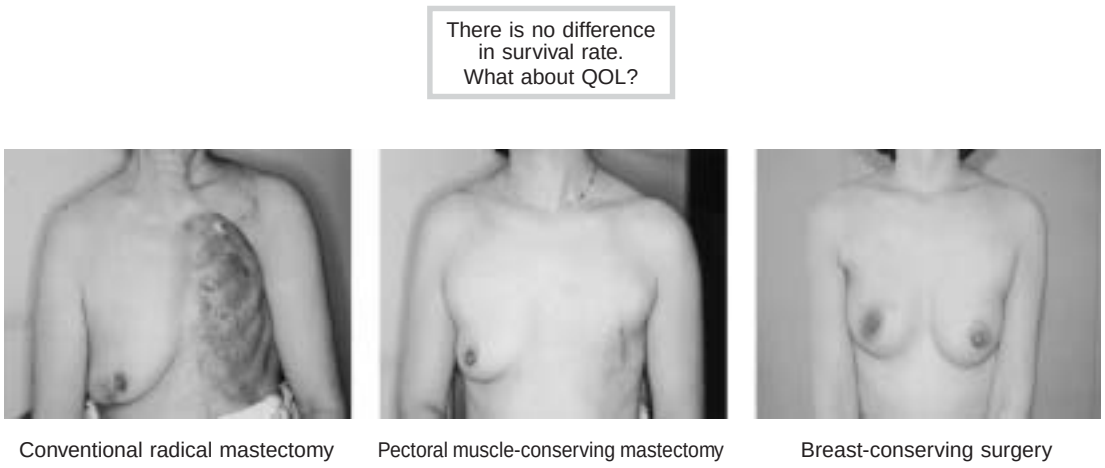


Fig. 1 Types of breast cancer surgery

involving dissection of parasternal and supraclavicular lymph nodes was attempted, allowing perfection of en bloc resection be pursued. However, prospective randomized controlled trials demonstrated the absence of any significant difference in survival rate between conventional radical mastectomy and extended radical mastectomy. As a result, the latter surgery associated with greater damage was performed less and less.

Later, advances in lymph flow research showed that en bloc resection is possible even if pectoral muscles are preserved. In this context, the Patey's operation preserving the pectoralis major muscle and the Auchincloss's operation preserving the pectoralis major and minor muscles were developed, and termed modified mastectomy. Prospective randomized controlled trials confirmed survival rates to be equal after conventional radical mastectomy and modified mastectomy. Subsequently, modified mastectomy took the place of conventional radical mastectomy as the standard surgery.

Thus, surgical techniques for the treatment of breast cancer have been evaluated in prospective randomized controlled trials, and less invasive standard surgery has been established. However, these are mastectomy techniques, and surgical therapy did not contribute significantly to improvement of QOL until the advent of breast-conserving therapy (Fig. 1).

2. Development of breast-conserving therapy

Breast-conserving surgery which allows the breast to be preserved was reported occasionally in the 1950s, when radical mastectomy was most common. In these cases, tumorectomy alone was performed in patients who rejected mastectomy or in those who were in a poor general state, and the results were not as poor as expected.

Initially, many surgeons disregarded these reports because they thought that the reports opposed en bloc resection, the basic surgery for cancer. However, similar reports subsequently appeared. Therefore, for the purpose of verification, six prospective randomized controlled trials of breast-conserving surgery and mastectomy were carried out in Western countries. These six clinical trials demonstrated no difference in survival rates between these two types of surgery and that radiotherapy to the breast after breast-conserving surgery effectively reduced the incidence of local recurrence.

In addition, breast conservation disclosed new biological properties of breast cancer, which overthrew Halsted's hypothesis. Namely, breast cancer is a systemic disease, and the

Table 1 Indications for Breast-conserving Therapy (1999 Breast-conserving Therapy Guidelines Proposed by the Japanese Society of Breast Cancer)

1. The tumor measures 3.0 cm or less*.
2. There are no findings indicative of extensive intraductal spread with various diagnostic imaging modalities (e.g., extensive malignant calcification on mammography).
3. Lesions are not multiple.
4. Irradiation is feasible. Thus, the following are excluded in principle.
   a) Concomitant serious collagen disease
   b) A history of irradiation to the ipsilateral chest
   c) Patients refuse irradiation
5. The patient requests breast-conserving therapy.

Note: *If a patient who has a tumor measuring more than 3.0 cm strongly desires this therapy, due consideration of preoperative and postoperative treatments is desirable for implementation of the therapy.

method of local treatment does not influence patient survival. This serves as the rationale for current breast cancer treatment, in which systemic drug therapy is regarded as important.

3. Changes in breast cancer surgery in Japan

In Japan, breast cancer specialists have been rare, and general surgeons have been performing surgery for breast cancer. Under these peculiar circumstances, believers in Halsted's hypothesis, i.e., the basic en bloc resection, predominated among surgeons dealing with breast cancer, and radical mastectomy and extended radical mastectomy remained common even after publication of the results of the aforementioned clinical trials in Western countries.

Breast-conserving therapy was introduced in some institutions in the mid 1980s in Japan. However, there were various protocols with inconsistent indications, surgical techniques, and radiotherapy, and there was no tendency or system to resolve these issues with clinical trials, unlike in Western countries.

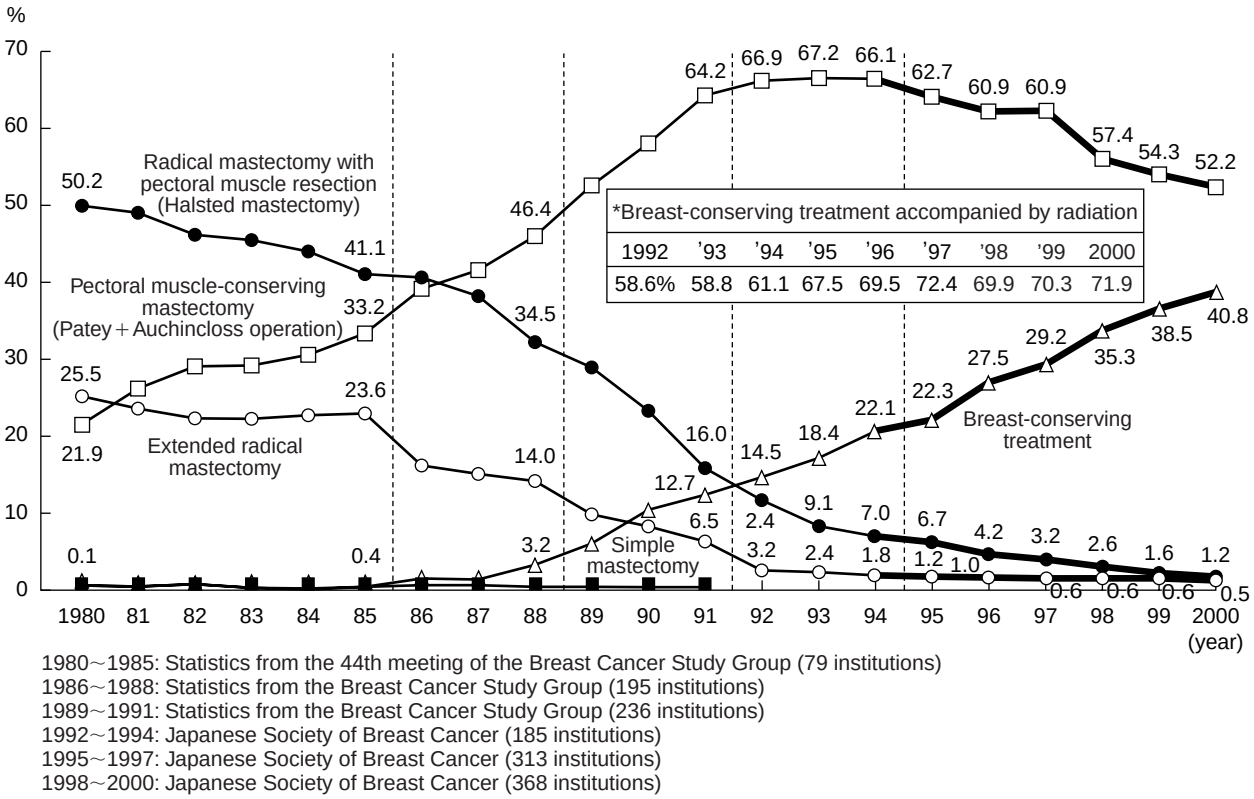
In 1989, a study group (led by Fujio Kasumi, Cancer Institute Hospital, Japanese Foundation for Cancer Research) was set up on the basis of a grant in aid for research on cancer from the Ministry of Health and Welfare. With the understanding that a prospective randomized controlled trial with mastectomy was no longer possible, the study group aimed at collection of cases under a uniform protocol to confirm the safety of this therapy. The initial protocol prescribed that breast-conserving therapy be combined with radiotherapy in principle, and that it was indicated for patients with a breast tumor measuring 2 cm or less in diameter by palpation and without metastasis to axillary lymph nodes on clinical examination. This study group was handed over to Koyama's group (led by Hiroki Koyama, Center for Adult Diseases, Osaka) and, then, to Sakamoto's group (led by Goi Sakamoto, Cancer Institute Hospital, Japanese Foundation for Cancer Research).[1,2] Based on the results of their research, the Japanese Society of Breast Cancer established the indications for breast-conversing therapy shown in Table 1.[3]

At present, investigations are underway by this study group, with the aim of eliminating restrictions on tumor size with the aid of preoperative chemotherapy and plastic surgery (Table 2).

Changes in breast cancer surgery in Japan according to the statistics reported by the Japanese Society of Breast Cancer are shown in Fig. 2. After 1989, when the protocol proposed by Kasumi's group was published, the use of breast-conserving therapy began to increase, reaching about 40% in 2000. Approximately 70% of such cases underwent combined radiotherapy. Among mastectomy techniques, the

Table 2 History of Breast-conserving Therapy Studies in Japan

Theme of the study (supported by a grant-in-aid for research on cancer from the Ministry of Health and Welfare)	Year	Indications		
		Tumor size	Lymph nodes	Combined therapy
Study of breast-conserving therapy for breast cancer	1989	2 cm or less	No metastasis	Postoperative radiotherapy Postoperative adjuvant therapy
Study demonstrating the safety of breast-conserving therapy	1991			
Study on extended indications for breast-conserving therapy based on the properties of intraductal tumor spread	1993	3 cm or less	No restrictions	
Study on extended indications for breast-conserving therapy in combination with pre- and postoperative therapy	1995			
Study on extended indications for breast-conserving therapy and prevention of postoperative recurrence by combining pre- and postoperative therapy	1997	No restrictions		Postoperative radiotherapy Postoperative adjuvant therapy Preoperative chemotherapy Plastic surgery



1980～1985: Statistics from the 44th meeting of the Breast Cancer Study Group (79 institutions)
1986～1988: Statistics from the Breast Cancer Study Group (195 institutions)
1989～1991: Statistics from the Breast Cancer Study Group (236 institutions)
1992～1994: Japanese Society of Breast Cancer (185 institutions)
1995～1997: Japanese Society of Breast Cancer (313 institutions)
1998～2000: Japanese Society of Breast Cancer (368 institutions)

Fig. 2 Changes in surgical techniques for the treatment of breast cancer in Japan (Japanese Society of Breast Cancer)

modified mastectomy became dominant, and conventional radical mastectomy and extended radical mastectomy were barely used.

4. Breast-conserving therapy and QOL

The ultimate goal of breast conservation is a therapeutic outcome equivalent to that of mastectomy and improved QOL derived from cosmetic satisfaction with the post-therapy breast. Before breast cancer surgery, the surgical technique is decided, attaching importance to patient preference after providing information on mastectomy and breast-conserving therapy. The actual percentage choosing breast-conserving therapy is not as high as medical providers might expect. In the case of our institution, although we have aggressively dealt with breast-conserving therapy since we joined the above study group, the percentage of patients who underwent breast-conserving therapy has reached a plateau at 40–50% of all breast cancer surgery cases. This is because the choice of this technique is complicated by cosmetic and psychological satisfaction, risk of local recurrence, and anxiety about radiotherapy for prophylaxis against recurrence.

We carried out a questionnaire survey of 1,101 patients who underwent breast-conserving therapy at 11 institutions participating in the above study group.[4] There were 911 respondents, for a response rate of 82.7%, and 883 respondents were evaluable. To the question "What do you now think about having undergone breast-conserving therapy, considering it comprehensively?", 41.2% of the respondents answered "very satisfied", and 56.8% answered "practically satisfied". These two groups accounted for 98% together, showing a high degree of overall satisfaction among patients who underwent breast-conserving therapy. On the other hand, many had anxiety about local recurrence (85.5%) and radiotherapy (85.4%). These statistics did not necessarily represent evaluation of QOL after breast-conserving therapy because there was no control group of mastectomy patients. However, the results disclosed the mentality of patients who were both satisfied with having avoided loss of the breast and anxiety about recurrence.

Patient QOL after breast-conserving therapy should be discussed in comparison with that after mastectomy. The current technique of mastectomy preserves pectoral muscles and the nerves innervating them. Therefore, it seems that there is little difference in outcome from breast-conserving therapy in terms of physical and functional aspects. Attention is currently focused on how avoidance of breast loss affects mental/psychological and social factors for the patient and whether breast-conserving therapy is superior to mastectomy from the viewpoint of overall QOL.

In Western countries, full scale research in this field was launched after 1980. The results of many studies have shown that there is no obvious difference between breast-conserving therapy and mastectomy because the former is not advantageous from the psychological aspect including fear of breast cancer recurrence, although the former is superior to the latter in terms of well-maintained body image and sexual function (Table 3).[5,6]

Problems in Studies of QOL

Previous studies involved the following problems, and contradictory results might be attributable to these problems: 1) the study population was small; 2) inclusion criteria were not definite; 3) the study was not randomized and controlled; 4) the statistical procedures including handling of defective data were not standardized; 5) the way informed consent was obtained was unclear; 6) the timing, frequency, and interval of survey were not standardized; and 7) the reliability and validity of the questionnaire was not verified.

Among these factors, the most important is the questionnaire. To assess QOL accurately, the questionnaire must include specific items related to the cancer in question as well as the four factors, i.e., physical, functional, mental/

Table 3 Comparison of Breast-conserving Therapy and Mastectomy

Investigator	Year of publication	No. of subjects		Choice of treatment	No. of investigations (timing)	Satisfaction with cosmetic outcome	Satisfaction with sexuality	Psychological influences	Fear of recurrence	Physical influences	Overall QOL
		Breast-conserving therapy	Mastectomy								
Sanger	1981	20	20	Patient's choice	1 (15–16 months)	○	?	△	?	?	?
Bartelink	1984	114	58	Random assignment	1 (24 months)	○	○	?	○	?	?
Steinberg	1985	21	46	Patient's choice	1 (14 months)	○	○	△	?	△	?
Taylor	1985	26	40	Patient's choice	1 (25.5 months)	○	○	○	?	?	?
de Haes	1986	21	17	Random assignment	1 (11–18 months)	○	△	△	△	△	△
Fallowfield	1986	48	53	Random assignment	1 (15.2–16.7 months)	?	△	●	?	?	?
Baider	1986	32	32	Patient's choice	1 (17.2–21.2 months)	?	△	△	?	?	?
Kemeny	1988	25	27	Random assignment	1 (18 months)	○	○	○	○	△	?
Wolberg	1989	41	78	Patient's choice	2 (4–8 months: 16 months)	△	?	△	?	△	△
Wellisch	1989	22	28	Patient's choice	1 (21 months)	○	○	△	△	△	?
Margolis	1990	32	22	Patient's choice	1 (38–49 months)	○	○	○	?	?	?
Levy	1992	90	39	Patient's choice	3 (immediately after: 3 months: 15 months)	?	?	●	?	?	△
Granz	1992	52	57	Patient's choice	3 (3 months: 6 months: 12 months)	○	△	△	△	△	△
Lasry	1992	79	44	Random assignment	1 (40–42 months)	○	△	△	△	?	?
Lee	1992	85	88	Random assignment	2 (3 months: 12 months)	○	△	△	?	?	?
Schain	1994	76	60	Random assignment	3 (6 months: 12 months: 24 months)	○	○	○	△	?	?
Omne -Ponten	1994	26	40	Patient's choice	1 (72 months)	△	?	△	△	?	?
Shimozuma	1996	22	33	Patient's choice	3 (0–2 months: 3–12 months: 13–24 months)	?	?	●	?	△	△
Inami	1997	90	123	Patient's choice	4 (3 months: 6 months: 12 months: 24 months)	○	?	○	△	△	?
Poulsen	1997	87	97	Random assignment	1 (15–62 months)	○	○	○	?	△	?
Curran	1998	127	151	Random assignment	1 (25–36 months)	○	?	?	△	?	?

○ Breast-conserving therapy superior ● Breast-conserving therapy inferior △ No difference ? Not examined

psychological, and social aspects, and the reliability and validity of the questionnaire must be statistically verified. Otherwise, the quality of the study must be regarded as being too low to allow international comparisons or comparisons with previous data. At present, reliable questionnaires available in Japan are that proposed by Kurihara's group, Ministry of Health and Welfare, and the Japanese versions of the EORTC QLQ-C3, FLIC, and FACT.[7)]

Since it became apparent that breast cancer has the properties of a systemic disease, limitations and indications for surgery, one form of local therapy, have been reconsidered. Avoidance of axillary lymph node dissection, using sentinel lymph node biopsy as an index, is also under consideration. The importance of QOL as a measure for such new treatment to be societally accepted appears to be increasingly recognized. However, the QOL concept has a personal aspect based on subjective ideas, and generalization of this concept requires further discussion.

Conclusion

A century has elapsed since radical mastectomy was developed, allowing breast cancer to be cured. Pursuing improvement of therapeutic results, surgical treatment of breast cancer has now evolved into breast-conserving therapy through extended radical mastectomy, a challenge to the limits of surgical therapy. The history of surgery for breast cancer is a history of choosing less invasive, limited surgical therapies that raise hopes of improved QOL.

Breast-conserving therapy allows breast preservation and achieves survival rates equivalent to those of mastectomy. This suggests that breast-conserving therapy would be superior to mastectomy in terms of QOL. However, previous studies have shown that the assumed superiority might merely be an illusion on the part of medical providers. More specifically, excluding the cosmetic issue, the superiority of breast-conserving therapy has not been demonstrated in terms of physical, functional, mental/psychological, and social factors. Possible disease recurrence within the preserved breast and anxiety about radiotherapy for preventing such recurrence are major factors diminishing the advantages of this procedure. This shows that provision of accurate information before choosing the therapeutic strategy and preparation of an adequate system for supporting the patient mentally and physically are essential for QOL improvement.

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Chemotherapy and Hormone Therapy for Breast Cancer: Current Status and Perspective

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Yoshinori ITO

Acting Chief, Department of Medical Oncology, Cancer Institute Hospital

Abstract: Chemotherapy or hormone therapy should be properly employed depending on the stage of breast cancer. The aim of therapy differs according to the stage of the disease; for example, palliation of symptoms or prolongation of life in metastatic diseases, enhancing the curative rate in adjuvant therapy, or increasing the rate of breast conservation during neoadjuvant treatments. Compared to classical CMF (cyclophosphamide, methotrexate and fluorouracil), chemotherapy, regimens containing anthracyclines, such as doxorubicin or epirubicin, are standard for metastatic, adjuvant and neoadjuvant cases. Recently, the benefits of taxans (docetaxel and paclitaxel) have been established for metastatic breast cancer. In hormone-receptor positive patients, tamoxifen is absolutely standard for metastatic or adjuvant cases. Luteinizing hormone-releasing hormone agonists or aromatase inhibitors are also useful. Other promising agents include trastuzumab for HER2/neu-positive patients and bisphosphonate for patients with bone metastasis. The benefits of systemic therapy, however, are limited and relative compared to the risk of toxicity. The benefits of chemotherapy, in particular, are occasionally nearly equal to the risk. Therefore, correct information on the benefits and risks of treatment must be given to patients to enable them to make a fully informed decision as to which therapy they wish to pursue.

Key words: Breast cancer; Chemotherapy; Hormone therapy; Adverse reactions

Introduction

Breast cancer often involves the regional lymph nodes and is frequently associated with small distant metastases from a relatively early stage. When the cancer is confined to the site of origin, local treatment by surgery alone or surgery combined with radiotherapy may lead

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to complete cure;[1)] at this early stage, breast cancer can be regarded as a local disease. However, as mentioned above, micrometastasis occurs relatively early in the course, followed by overt metastasis. When micrometastasis occurs, the disease is no longer curable by surgery alone, and recurrence is often noted. Anticancer drugs and hormones exert systemic effects, and act on cancer cells throughout the body, including those in micrometastatic foci. However, drug therapy alone is not sufficient to effect a complete cure of the disease — this is one of its important limitations. It is therefore desirable to supplement local treatment with drug therapy for systemic treatment of breast cancer, employing proper timing and methodology.

Expected Benefits and Risks of Treatment

The goal of drug therapy varies according to the stage of breast cancer. One of the following three situations generally exists.

(1) Distant metastasis is present, so that definitive cure is not likely after drug therapy; only alleviation of symptoms and some prolongation of life may be expected.
(2) No distant metastasis, and surgery is feasible; postoperative adjuvant chemotherapy may increase the cure rate.
(3) The primary tumor mass is large, but there is no distant metastasis. In this case, preoperative chemotherapy may allow breast-conserving surgery.

Thus, the goal of drug therapy varies according to the stage of the disease, and it is very important to clearly recognize the goal. The final decision regarding the choice of treatment and continuation of treatment must be made by weighing the benefits and risks (adverse reactions) of the treatment. For example, many patients are ready to receive treatment that has been shown to yield a higher cure rate, but may cause hair loss and nausea. On the other hand, some patients may find it difficult to tolerate the severe adverse effects of anticancer drug therapy for prolonged periods if it becomes apparent that complete cure is not likely. The physician-in-charge should be fully aware of the expected benefits and risks of the treatment and explain these in clear terms to the patient. This may not be difficult if the expected benefits of treatment outweigh the risks. However, when this is not the case, since there is little difference between benefit and risk regarding anticancer drug therapy, the judgment should depend on the decision of the individual. Each patient reserves the right to decide whether or not to receive the treatment, and to choose any of the therapeutic options available; the final decision should therefore be left to the judgment of the patient. To facilitate such judgment on the part of the patients, medical care providers should provide accurate information as clearly as possible to the patients.

Outline of Drug Therapy

In general, hormone therapy exerts its effects gradually, and elicits only mild adverse reactions. During hormone therapy, improvement may be preceded by a temporary aggravation, the so-called flare phenomenon. On the other hand, chemotherapy exerts its effects more promptly, and often elicits severe adverse reactions. Currently, the therapeutic usefulness of both hormone therapy and anticancer drug therapy remains established. Combined chemotherapy and hormone therapy has been attempted, but its superiority has not yet been clearly demonstrated. In general, either chemotherapy or hormone therapy is administered first, and the other alternative is used thereafter, if required.

When the patient is estrogen-receptor-positive (ER-positive) and/or progesterone-receptor-positive (PgR-positive), hormone therapy is expected to be effective. When a patient with metastatic breast cancer is classified as hormone-sensitive based on the receptor expression, hormone therapy, as a rule, should be administered first, to be replaced by chemotherapy if resis-

Table 1 Representative Chemotherapeutic Regimens for Breast Cancer
Product names are shown in parentheses.

Classical CMF		
Cyclophosphamide (Endoxan®)	100 mg/body, p.o., d1–15	every 4 weeks
Methotrexate (Methotrexate®)	40 mg/m^2, i.v., d1, d8	
5-Fluorouracil (5-FU®)	500 mg/m^2, i.v., d1, d8	
Intravenous CMF		
Cyclophosphamide (Endoxan®)	600 mg/m^2, i.v., d1	every 3 weeks
Methotrexate (Methotrexate®)	40 mg/m^2, i.v., d1	
5-Fluorouracil (5-FU®)	600 mg/m^2, i.v., d1	
Modified intravenous CMF		
Cyclophosphamide (Endoxan®)	500 mg/m^2, i.v., d1, d15	every 4 weeks
Methotrexate (Methotrexate®)	40 mg/m^2, i.v., d1, d15	
5-Fluorouracil (5-FU®)	500 mg/m^2, i.v., d1, d15	
CAF (FAC)		
Cyclophosphamide (Endoxan®)	500 mg/m^2, i.v., d1	every 3 weeks
Adriamycin (Adriacin®)[a]	50 mg/m^2, i.v., d1	
5-Fluorouracil (5-FU®)	500 mg/m^2, i.v., d1, d8	
CAF		
Cyclophosphamide (Endoxan®)	100 mg/m^2, p.o., d1–15	every 4 weeks
Adriamycin (Adriacin®)[a]	30 mg/m^2, i.v., d1, d8	
5-Fluorouracil (5-FU®)	500 mg/m^2, i.v., d1, d8	
Docetaxel (Taxotere®)[b]	60–70 mg/m^2, i.v., 1h	every 3 weeks
Paclitaxel (Taxol®)[c]	175–210 mg/m^2, i.v., infusion over 3 h	every 3 weeks

[a] The total dose of adriamycin should be limited to 450 mg/m^2, because of the cumulative cardiotoxicity of the drug.
[b] To prevent allergy and edema, dexamethasone (Decadron) 8 mg/day (in two divided doses) should be administered orally for 3 days, starting before chemotherapy.
[c] To prevent allergy, intravenous dexamethasone (Decadron), 20 mg, should be administered twice, i.e., 12–14 h, and 6–7 h before the start of therapy, and oral diphenhydramine (Restamin), 50 mg, and intravenous ranitidine (Zantac), 50 mg, should be administered 30 min. before the start of therapy.

tance to hormone therapy become evident.

For postoperative adjuvant therapy, chemotherapy should be given first for a period of 3–6 months, and hormone therapy thereafter. In the case of therapy with tamoxifen, a representative hormonal drug, it has been recommended that the drug be continued for 5 years.[2] For preoperative chemotherapy, anticancer drugs that are expected to have prompt effects are often used, aimed at tumor mass reduction. Such chemotherapy is usually indicated in patients with localized advanced cancer, as in stage IIIA or IIIB. In recent years, however, it has also been given for earlier stages of breast cancer. Usually, 4–6 courses are used for preoperative chemotherapy. When indicated for patients in high risk, postoperative chemotherapy may also be administered, followed by hormone therapy.

Since patient survival has been reported to be similar, regardless of whether chemotherapy is administered preoperatively or postoperatively, the aim of preoperative chemotherapy is to facilitate breast conservation. In general, if preoperative chemotherapy reduces the tumor diameter to less than 3 cm, the lesion becomes amenable to breast-conserving surgery. Another advantage of preoperative chemotherapy is that it becomes evident sooner than later whether or not the tumor is responsive to anticancer chemotherapy. With this information, the subsequent course of anticancer chemotherapy can be altered as necessary. Table 1 shows representative anticancer chemotherapies for

breast cancer.

Hormone Therapy for Metastatic Breast Cancer

Many breast cancers show estrogen-dependent proliferation. Administration of antiestrogens can, therefore, be expected to cause tumor mass reduction. The most well established drug for hormone therapy is tamoxifen (Nolvadex®). This is a first-line drug for the treatment of breast cancer in postmenopausal patients. If the patient is ER- and/or PgR-positive, hormone therapy is indicated. Tamoxifen is administered orally at the dose of 20 mg/body every morning. In both ER- and PgR-positive cases, the response rate to tamoxifen therapy is 50–70%. The time to progression is about 6 months, and the duration of response is 12–18 months. Tamoxifen does not elicit such severe adverse reactions as anticancer chemotherapeutic drugs. Cautious watchfulness is necessary for rare adverse reactions, including endometrial cancer, cerebrovascular disease, pulmonary embolism, venous thrombosis, and cataract. These disorders occur in about 5–6 of 1,000 patients. Periodic gynecological examination is recommended for early detection of endometrial cancer. Toremifene (Fareston®), whose actions on the endometrium are weaker than those of tamoxifen, is known to be as effective as tamoxifen, but whether or not it's administration is actually associated with reduced incidence of endometrial cancer has not yet been clearly established. When the patient has a history of embolism or thrombosis, other hormone therapy (aromatase inhibitors, as described below) would be desirable.

Second-line hormone therapy consists of treatment with the recently developed aromatase inhibitors. Aromatase is an estrogen-converting enzyme present in fat, liver and muscle tissue. Aromatase inhibitors suppress the production of estrogen in these peripheral tissues. In Japan, fadrozole (Afema®), an aromatase inhibitor, is commercially available. Afema is administered orally at the dose of 2 mg/body every morning. Adverse reactions such as nausea, vomiting, and hot flushes may occur, but these are mild. This class of drugs has been established for second-line therapy in postmenopausal patients with metastatic breast cancer. The therapy has been reported to be effective in 20–30% of patients who do not show the expected response to tamoxifen. Another drug of this class, anastrozole (Arimidex®), has become commercially available in Japan since February 2001.

Progesterone therapy is considered as third-line therapy. The mechanisms of actions of progesterone preparations have not been fully elucidated. In Japan, medroxyprogesterone acetate (Hysron H®, Provera®, a representative drug of this class, is used. This agent is administered orally at the dose of 600–1,200 mg/body daily. Weight gain may occur in 20–50% of patients, and obesity may interfere with the continuation of this drug. The drug may also be used as an appetite stimulant in patients with advanced disease who are cachexic. This therapy has been designated as third-line, because of the more severe adverse effects associated with its administration in comparison with those associated with tamoxifen or fadrozole therapy.

The estrogen balance in the body changes dramatically after menopause. Specifically, before menopause, the ovaries function actively to secrete abundant amounts of estrogen. After menopause, the ovarian activity decreases, with resultant fall in the estrogen levels. In premenopausal patients with breast cancer, secretion of estrogen from the ovaries must be inhibited. Ovariectomy has long been known to be effective in the treatment of breast cancer. At present, it is possible to competitively block follicle-stimulating hormone released from the pituitary, and thereby to inhibit the production of estrogen by the ovaries. Goserelin (Zoladex®) or leuprolide (Leuplin®), which are luteinizing hormone-releasing hormone analogues (LH-RH analogues), represent established drugs for the treatment of breast cancer in premenopausal women. Zoladex®, 3.6 mg, or Leuplin®,

3.75 mg, is injected subcutaneously once every 4 weeks. There are scarcely any adverse reactions, besides hot flushes. In premenopausal patients, therefore, direct antitumor effect by lowering the estrogen levels is aimed at by using combined LH-RH-analogue and tamoxifen therapy. Recently, the usefulness of this therapeutic strategy has been demonstrated, and it is now being established as the first-line hormone therapy for premenopausal patients.

Chemotherapy (Anticancer Drug Therapy) for Metastatic Breast Cancer

Following the development of alkylating agents and antimetabolites, the usefulness of therapy with CMF, a combination chemotherapeutic regimen, was first established. This drug combination consists of cyclophosphamide (Endoxan®), methotrexate (Methotrexate®), and 5-fluorouracil (5-FU®). The response rate, in terms of complete response or partial response, was 40–50%. Subsequently, anthracyclines were developed. Representative anthracyclines include adriamycin (Adriacin®) and epirubicin (Farmorubicin®). CAF, a drug combination containing adriamycin, and FEC, a drug combination containing epirubicin, are now standard chemotherapeutic drug regimens. The response rate to these regimens is 50–60%, which is significantly higher than that to CMF therapy. The duration of response is 6–12 months, and the mean length of survival following either CAF or FEC therapy is 2 years. The 5-year survival rate may be 10–20%, but the 10-year survival rate is only around 3–4%. Therefore, complete cure is difficult in most cases.[3)]

In a breakthrough study, high-dose chemotherapy in combination with hematopoietic stem cell transplantation was attempted. Standard-dose chemotherapy is associated with a complete response rate of only 10–20%, whereas high-dose chemotherapy yields a corresponding percentage on the order of 40%. However, the disease often recurs, and complete cure is rarely achieved. Until now, distinct superiority of this treatment over the conventional chemotherapeutic regimens has not been clearly established; high-dose chemotherapy still remains in the investigational stage, requiring further designing and study. Cancer Institute Hospital is currently conducting studies of high-dose chemotherapy combined with gene therapy.

In recent years, the efficacy of the tubulin inhibitors, taxanes, has been established.[4)] Taxanes include paclitaxel (Taxol®) and docetaxel (Taxotere®). Docetaxel is given at the dose of 60–70 mg/m^2 once every three weeks; the response rate is about 30–50%. Paclitaxel is given by intravenous infusion over 3 h at the dose of 175–210 mg/m^2; the response rate is on the order of 30%. The greatest advantage of taxanes is that they are effective in anthracycline-resistant cases. To reduce the incidence and severity of neutropenia and to provide a higher dose density, weekly administration has been tried. The dose is 30–35 mg/m^2 for docetaxel, and 80 mg/m^2 (drip infusion over 1 h) for paclitaxel. Although taxanes are effective as monotherapy, combination regimens with anthracycline are now being extensively studied. A large-scale randomized trial to compare with adriamycin + Taxotere® (AT) and adriamycin + cyclophosphamide (AC) revealed that the former was superior to the latter in terms of the response rate and time to progression. AT was also superior to CAF in terms of the response rate and time to progression. Combinations of anthracyclines and taxanes may become one of the standard chemotherapeutic regimens for cancer of the breast in the future.

What is the appropriate duration of chemotherapy? Should chemotherapy be continued for prolonged periods? Therapeutic results were compared between patients in whom the treatment was continued and those in whom the treatment was not continued after obtaining a complete response, partial response or no response to the initial therapy. The results revealed that the time to progression was longer in patients in whom the therapy was

continued, however, there was no overall difference in the length of survival between the two groups. Thus, while prolongation of chemotherapy may not necessarily result in complete cure, it is able to delay disease progression. Therefore, decisions in the clinical setting may be made as follows. If there are scarcely any adverse reactions and the patient can visit the hospital periodically without much difficulty or suffering, prolonged chemotherapy may be considered. If, on the other hand, there are severe adverse reactions, therapy may be discontinued temporarily, and then resumed when the disease shows progression. A possible strategy is to administer chemotherapy at longer intervals. Any decision should be arrived at only after discussing in detail the advantages and disadvantages of the available treatment options with the patient.

Adverse Reactions of Anticancer Drugs and the Choice of Regimen

The major adverse reactions of anticancer drugs are nausea/vomiting and hair loss. Although adriamycin (or epirubicin) and taxanes are extremely useful drugs, therapy with which is associated with the highest response rates, both cause severe hair loss. There is no effective prophylaxis available against this side effect. In general, hair loss begins about 2 weeks after the start of medication, and becomes substantial by 3–4 weeks. Short hair reappears about 3 months after withdrawal of the medication, and hair growth to the pretherapeutic level occurs after about 6 months after the drug withdrawal. Hair loss, once it sets in, continues throughout the duration of the chemotherapy, necessitating the use of a wig. On the other hand, although there are variations in severity among individuals, nausea/vomiting usually last only for about 2–5 days after an intravenous dose, and the patient's condition usually improves thereafter. CMF therapy or oral fluorouracil derivatives are usually associated with very slight hair loss and mild nausea. The CAF and FEC regimens may cause severe hair loss and severe nausea/vomiting. With taxanes, while the hair loss may be severe, nausea/vomiting is usually mild. In cases of metastatic breast cancer, chemotherapy does not greatly influence the survival, although the response rates to different regimens may vary. Therefore, in patients who do not want to risk hair loss, chemotherapy beginning with the CMF or oral fluorouracil regimen may be considered. However, if hair loss is acceptable to the patient, CAF, FEC or taxanes should be administered as first-line therapy. In such cases, who are susceptible to nausea/vomiting, taxane therapy should be preferred over the other two regimens as first-line therapy.

Administration of CAF, FEC and taxane regimens is often associated with leukopenia. Taxane + adriamycin therapy is especially likely to cause leukopenia. Treatment-related death due to sepsis should be avoided in these cases. If a patient with a neutrophil count of less than $1{,}000/mm^3$ develops fever, intravenous infusion of a broad-spectrum antibiotic should be initiated promptly, along with administration of granulocyte colony-stimulating factor (Neutrogin®, Gran®, Neu-up®). Patients should be instructed to take an oral antibiotic promptly if they develop a fever of 38°C at home. Adriamycin also exerts cardiotoxicity, and its total dose should be limited to $450\,mg/m^2$. To prevent docetaxel-induced allergy and edema, oral dexamethasone (Decadron®), 8 mg/day (in two equally divided doses), should be administered for 3 days beginning from the day before the initiation of docetaxel therapy. To prevent allergic reaction to paclitaxel, dexamethasone (Decadron®), 20 mg, should be administered intravenously twice, i.e., 12–14 h, and 6–7 h, before the start of paclitaxel therapy, and oral diphenhydramine (Restamin®), 50 mg, and intravenous ranitidine (Zantac®), 50 mg, should be administered 30 min before the start of therapy.

Postoperative Adjuvant Therapy

For hormone therapy and chemotherapy as

Table 2 Adjuvant Systemic Treatment for Patients with Operable Breast Cancer
(Cited from the Consensus Panel of St. Gallen, 2001)

Risk Group	Treatment According to Responsiveness to Endocrine Therapies*[1]			
	Endocrine-Responsive		Endocrine-Nonresponsive	
	Premenopausal	Postmenopausal	Premenopausal	Postmenopausal
Node-negative, minimal/low risk	Tamoxifen or none	Tamoxifen or none	Not applicable	Not applicable
Node-negative, average/high risk	Ovarian ablation (or LH-RH analogue) + tamoxifen [± chemotherapy*[2]], or Chemotherapy + tamoxifen*[2] [± ovarian ablation (or GnRH analog)] or Tamoxifen, or Ovarian ablation (or GnRH analog)	Tamoxifen, or Chemotherapy + tamoxifen*[2]	Chemotherapy*[3]	Chemotherapy*[3]
Node-positive	Chemotherapy + tamoxifen*[2] [± ovarian ablation (or GnRH analog)], or Ovarian ablation (or GnRH analog) + tamoxifen [± chemotherapy*[2]]	Chemotherapy + tamoxifen,*[2] or Tamoxifen	Chemotherapy*[3]	Chemotherapy*[3]

NOTE. Brackets [ ] indicate questions pending answers from ongoing clinical trials. Regarding GnRH, research was conducted using goserelin.

*[1] See footnote in Table 3 regarding responsiveness to endocrine therapies.

*[2] The addition of chemotherapy is considered an acceptable option based on evidence from clinical trials. Considerations about a low relative risk, age, toxic effects, socioeconomic implications, and information on the patient's preference might justify the use of tamoxifen alone. For patients with endocrine-responsive disease, whether tamoxifen should be started concurrently with chemotherapy of delayed until the completion of chemotherapy must await the result of ongoing trials.

*[3] For patients with endocrine-nonresponsive disease, questions of timing, duration, agent, dose, and schedules of chemotherapy are subjects for research studies.

postoperative adjuvant therapy in breast cancer, the recommendations made by the Consensus Panel at St. Gallen in 2001 have generally been accepted (Tables 2 and 3).[5] In addition, the consensus statement by the US National Institute of Health (NIH) has been available on the Internet since November 2000 (http://odp.od.nih.gov/consensus/cons/114/114_intro.htm).

The most important prognostic factor in patients with breast cancer is the lymph node status. Chemotherapy is basically indicated for patients with positive axillary lymph node metastasis, and hormone therapy should be added if such patients are ER- and/or PgR-positive. Even if no axillary lymph node metastasis is detected, aggressive chemotherapy should be considered if the risk of metastasis is deemed to be high. In patients with positive lymph nodes, surgery followed by chemotherapy reportedly yields a 15.4% improvement in 10-year disease-free survival rate in patients younger than 50 years old, and a 5.4% improvement in absolute survival rate in patients between 50 and 69 years of age. In cases where lymph node metastasis is not detected, chemotherapy should be considered in an average/high risk group. Chemotherapy is not indicated in the minimal/low-risk group.

Chemotherapy As Postoperative Adjuvant Therapy[6,7]

An Italian group reported the long-term (20 years) results of CMF therapy. CMF is considered to be one of the standard chemotherapeutic regimens, because it yields definite improvement in the disease-free survival rate as compared with the results in untreated patients. A meta-analysis revealed that a regimen containing an anthracycline was better than CMF. How-

Table 3 New Definition of Risk Categories for Patients with Node-Negative Breast Cancer
(Cited from the Consensus Panel of St. Gallen, 2001)

Risk Category	Endocrine-Responsive*[1]	Endocrine-Nonresponsive*[1]
Minimal/low risk*[2]	ER- and/or PgR-positive, and all of the following features: pT*[3] ≤ 2 cm, and Grade 1*[4], and Age*[5] ≥ 35 years	Not applicable
Average/high risk	ER- and/or PgR-positive, and at least one of the following features: pT*[3] > 2 cm, and Grade 2–3*[4], and Age*[5] < 35 years	ER- and PgR-negative

Abbreviations: ER, estrogen receptor; PgR, progesterone receptor.

*[1] Responsiveness to endocrine therapies is related to expression of ER and PgR in the tumor cells. The exact threshold of ER and/or PgR staining (with currently available immunohistochemical methods), which should be used to distinguish between endocrine-responsive and endocrine-nonresponsive tumor, is unknown. Even a low number of cells stained positive (as low as 1% of tumor cells) identify a cohort of tumors having some responsiveness to endocrine therapies. Probably, as it typical for biologic systems, a precise threshold does not exist. However empirically chosen, approximately 10% positive staining of cells for either receptor might be considered as a reasonable threshold, accepted by most. Furthermore, it is clear that the lack of staining for both receptors confers endocrine nonresponsiveness status.

*[2] Some Panel members recognize lymphatic and/or vascular invasion as a factor indicating greater risk then minimal or low. On the other hand, mucinous histologic type is associated with low risk of relapse.

*[3] Pathologic tumor size (i.e., size of the invasive component).

*[4] Histologic and/or nuclear grade.

*[5] Patients with breast cancer at young age have been shown to be at high risk of relapse.

ever, the absolute differences between the two were small, with an overall improvement of 3.2% in the 5-year recurrence-free survival rate and 2.7% in the 5-year overall survival rate.

Recently, it has been shown that 4 courses of adriamycin + cyclophosphamide therapy followed by 4 courses of paclitaxel therapy given as postoperative adjuvant therapy, prolong the recurrence-free survival and overall survival rates in patients with lymph node metastasis. The absolute benefit was slight, with a 4% improvement in the recurrence-free survival rate and 2% improvement in the overall survival rate. However, this study was a large-scale study covering more than 3,000 patients, and the differences were evidently statistically significant. In USA, the use of paclitaxel for postoperative adjuvant therapy was approved in October 1999. It is expected that postoperative adjuvant therapy consisting of an anthracycline and a taxane will become established as a standard regimen in the near future.

Hormone Therapy As Postoperative Adjuvant Therapy[2,6)]

The usefulness of tamoxifen for postoperative adjuvant therapy has been widely recognized. A meta-analysis showed that its benefits were apparent across all age groups, and an approximately 50% decrease (odds ratio) in the risk of recurrence and 25% decrease (odds ratio) in the death rate, on the average, were reported. Tamoxifen therapy should be continued for at least 5 years. The risks and benefits of more prolonged therapy are now under investigation. Tamoxifen has been reported to be beneficial in patients who are ER- and/or PgR-positive; the higher the ER expression level, the greater the benefit. Conversely, the treat-

ment is of no benefit in patients who are both ER- and PgR-negative. Moreover, there tend to be adverse effects, so that tamoxifen should not be used in patients who are both ER- and PgR-negative.

Since estrogen secretion from the ovary is decreased in premenopausal patients, ovariectomy or LH-RH analogue therapy is considered as the basic policy. LH-RH analogue therapy combined with tamoxifen therapy have recently been shown to be equal to or superior in efficacy to CMF therapy. LH-RH analogue + tamoxifen therapy has also become a standard regimen for postoperative adjuvant therapy in premenopausal patients.

Future Drug Therapy

Trastuzumab (Herceptin®),[8] a monoclonal antibody directed against HER2, and bisphosphonates,[9] useful drugs for bone metastasis, are recently established treatments. Trastuzumab is effective in patients with metastatic breast cancer who are positive for HER2. A randomized trial has demonstrated that combined paclitaxel and trastuzumab therapy is superior to paclitaxel monotherapy, in terms of the response rate and length of survival. Comparative studies have begun to investigate the usefulness of trastuzumab in postoperative adjuvant therapy, as the drug appears to show promise. Like the relationship between ER expression and the beneficial effects of tamoxifen therapy, determination of HER2 expression is expected to be utilized widely for predicting the sensitivity to trastuzumab treatment, and incorporated into the treatment system of breast cancer.

Bisphosphonates (Aredia®, Onclast®, Bisphonal®) interfere with invasion of the bone by osteoclasts. This kind of agents is useful for patients with hypercalcemia. In recent years, the beneficial effects of these agents on bone metastasis have been studied, and clinical improvement of bone pain, improved QOL, and delay in the development of osseous complications, including bone fracture, have been demonstrated. Unfortunately, the National Health Insurance in Japan covers bisphosphonates used only for the treatment of hypercalcemia. Currently, studies on bisphosphonates as therapeutic drugs, or prophylactic agents to delay the development of bone metastasis, are underway, and these agents may soon be used clinically for such purposes.

Aromatase inhibitors, hormone agents which are equal or superior to tamoxifen, have also been developed, and their propriety as first-line therapy is now under investigation.

Conclusion

In choosing a drug treatment for breast cancer, it is important to clearly recognize the purpose of the treatment, namely whether it is used for metastatic breast cancer aimed at prolongation of life or amelioration of symptoms, as postoperative adjuvant therapy aimed at cure of the disease, or as preoperative therapy aimed at breast conservation, and to weigh the benefits and risks, bearing in mind the adverse reactions to the treatment, particularly hair loss, nausea/vomiting, and leukopenia. Implementation of drug therapy for breast cancer requires sufficient knowledge, appropriate judgment, and preparedness for management of adverse reactions. Drug therapy of breast cancer is advancing rapidly. As of January 2001, 432 hospitals are accredited in parallel with the accreditation of physicians and the specialist system. Consultation or referral of the patients to these experts could be encouraged.

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Current Status and Perspectives of Radiation Therapy for Breast Cancer

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Masahiro HIRAOKA, Masaki KOKUBO, Chikako YAMAMOTO and Michihide MITSUMORI

Department of Therapeutic Radiology and Oncology, Kyoto University Graduate School of Medicine

Abstract: Current status and perspectives of radiation therapy for breast cancer in Japan are reviewed. Breast conserving treatment, defined as a combination of conservative surgery for resection of the primary tumor, mostly with dissection of the axillary nodes, followed by radiation therapy for the eradication of residual microscopic disease in the breast has become prevalent, and clinical results reported are very encouraging. The indications and techniques for radiation therapy including boost irradiation are being discussed. A CT simulator, 3-dimensional treatment planning system, is considered to be essential to accomplish a sophisticated radiation therapy. The post-operative irradiation following mastectomy for locally advanced breast cancer has been highlighted in the recent positive results of prospective randomized trials. The role of radiation therapy for distant metastasis including bones and brain has been described. Finally, perspectives of radiation therapy for breast cancer is demonstrated.

Key words: Breast cancer; Breast conserving therapy; Radiation therapy; Postoperative irradiation

Introduction

Radiation therapy plays several roles in the management of breast cancer including: (1) radical irradiation in breast conserving treatment, (2) radical and palliative irradiation against locally advanced cancer, (3) palliative and radical irradiation against locoregional recurrent cancer, (4) prophylactic irradiation following mastectomy, and (5) palliative irradiation against distant metastasis, such as bone and brain. All of those contribute to improving patients' QOL. The significance of radiation therapy in breast conserving treatment, postoperative irradiation, and bone metastases will be outlined.

Significance of Radiation Treatment in Breast Conserving Therapy

Mastectomy has been standard therapy for breast cancer. For women, however, loss of a

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breast results in overwhelming psychological/emotional problems. Thus, supported by the patients' strong desire, breast conserving therapy was started in Europe in the 1950s. This type of therapy was conducted using radiation equipment that was inadequate, compared with what is currently available. However, equivalent results were achieved comparable to those obtained by mastectomy, and thereafter the treatment spread in the U.S. and Europe. In the 1970s and 1980s, a large-scale phase III clinical study comparing mastectomy and breast conserving treatment in patients with breast cancer showed that the rates of locoregional recurrence and survival in breast conserving treatment were comparable to those seen in mastectomy. "Conference on treatment of the early stage breast cancer" was held by the National Institute of Health (NIH) of the U.S.A. in June of 1990, and it was concluded that breast conserving therapy is preferable in most patients with Stage I and II cancer based on those clinical data. Since then, this therapy has been globally recognized as one of the standard treatments for breast cancer.

The breast conserving treatment is defined as a combination of conservative surgery for resection of the macroscopic lesion, and postoperative radiation therapy for the eradication of residual microscopic lesion. The more extensive the breast conserving surgery, the smaller the tumor cells remaining in the conserved breast, while the larger operation may undermine the cosmetic outcome. The aim of breast conserving therapy is to achieve comparable therapeutic outcomes to mastectomy, while providing the improvement of the patient's QOL. Based on the current status in the U.S. and Europe, the roles of radiation treatment in Japan will be expected to expand in the future, with smaller resections in conservative surgery and expanded indications for breast conserving therapy.

1. Indications and contraindications

In the U.S. and Europe, indications for breast conserving treatment are wide, and contraindications (most of them are not absolute but relative) should be considered further. In Japan also, an increasing number of institutes have adopted this policy. In these institutes, the ratio of breast conserving treatment is over 50%. The following conditions are unsuitable for breast conserving treatment.

(1) **Poor cosmetic outcomes**

Tumor size relative to breast size is important. Many institutes employ breast conserving therapy when the tumor size is more than 3 cm in diameter. It can be larger in a patient with large breasts. In addition, when the lesion is around the nipple-arela complex, lower cosmetic outcome is anticipated.

(2) **A high risk of complications**

For pregnant women, the priority is mastectomy because of the effects of radiation on the fetus. It has recently been reported that breast conserving treatment cannot be recommended for a patient with collagen disease which is likely to cause severe radiation damage. For a patient who previously experienced radiation therapy on the area of interest, mastectomy should be chosen.

(3) **High locoregional recurrence rate compared with mastectomy**

When multiple masses can be found by palpation or imaging modalities, or diffuse calcification can be found in mammography, mastectomy is recommended because of their high recurrence rate. Some reported that local recurrence rate is significantly high in patients with extensive intraductal component (EIC). It is reported that local recurrent rate is not increased when surgical margin is free of tumor cells.

2. Methods of radiation therapy

(1) **Treatment schedule**

The targets of irradiation are the conserved breast and the axilla. The axilla is not included if lymphoadenectomy is sufficient. However, if only a few lymph nodes are collected, the axilla should be included. There is controversy

regarding whether the supraclavicle or parasternal lymph nodes are included. They are often excluded because of the complexity involved in setting the irradiation target, the increased dose of radiation on the lung, and few reports showing the improvement of the results.

(2) **Irradiation of conserved breast**

Two opposing tangential irradiation is performed for the conserved breast. The volume of conserved breast to be treated should be decided for each case. Treatment planning based on a CT simulator is useful for this purpose. The effectiveness is especially high for patients with large breasts in which a part of the conserved breast is excluded in the conventional method, and for patients with a thick layer of subcutaneous fat.

Telecobalt or x-ray with 4 or 6 MV is used for tangential irradiation. Telecobalt can be used for medium sized or smaller breasts, however, problems may occur due to the higher dermal dose. If the distance between the inner edge and the outer edge of the irradiated site is over 20 cm, x-rays of more than 6 MV should be used. In this case, the dose on the surface of the mammary gland should be carefully checked. A bolus should be used when the x-ray is more than 10 MV, because of the decreased dose on the surface of the mammary gland.

A total of 45–50 Gy, 1.8–2 Gy per dose, is appropriate for the irradiation of a conserved breast. It is reported that the local recurrence rate is high in irradiation with less than 8 Gy per week.

(3) **Boost irradiation**

Boost irradiation is based on observations that most of the local recurrence develop from surrounding sites of the primary lesion, and that most of the remaining tumor is found around the primary lesion in a histopathological investigation of the specimen of the resected breast. The presence of tumor cells in the resected stump, and unclear information on the stump, are indications to perform boost irradiation. Boost irradiation is applied when tumor cells are found near the resected stump (within 5 mm from the resection site).

The target to be boosted should be carefully determined in each case. It should be determined based not only on operative wounds, but also on interview, imaging methods, and preferably the placement of a clip at the surgical margin. The target volume is the tumor bed with a safety zone of 1.5 cm for complete resections, and with a safety zone of 3 cm for incomplete resections. Irradiation with 2 Gy 5 times a week, a total of 10–20 Gy, is necessary, and more than 60 Gy including dose on conserved breast are delivered.

3. Treatment effects

Radiation therapy reduces the possibility of recurrence in breast. Table 1 shows the recurrence rate of surgery with and without radiation therapy in randomized trials.

We started breast conservation therapy from December 1987, and 1,491 patients with 1,515 breast cancers have been treated as of December 2000. Initial indications were patients that met the following 2 criteria: (1) tumor diameter is less than 2 cm, (2) distance between the inner edge and the outer edge of tumor is more than 3 cm. Subsequently, indications were expanded so that this treatment is now performed on all patients other than the previously mentioned contraindications. The patients ages ranged from 21 to 86 years with a mean of 49 years. There were 55 non-invasive cancers, 1,224 invasive cancers, 207 others, and 29 unidentified cancers. According to the clinical classification, there were 49 Tis, 7 0, 715 stage I, 697 stage II, 28 stage III, and 19 unidentified. According to the histological classification, 1 was 0, 1,183 stage I, 251 stage II, 51 stage III, and 29 unidentified.

The prevalent surgical procedure was quadrantectomy (sector excision of glandula mammaria) until December of 1992. Since then, wide excision has been performed in most cases. In many patients, axillary lymphadenectomy (resection of level I–III lymph nodes was

Table 1 Comparison of the Locoregional Recurrence Rate with and without Radiation Treatment

Author	Number of patients	Target	Operation method	Radiation treatment	Median follow-up period	Locoregional recurrence rate, radiation (−)	Locoregional recurrence rate, radiation (+)	*p* value
Veronesi *et al.*	579	T≤2.5 cm	Quadrant-ectomy	Conserved breast 50 Gy/25 fr./5 wks Boost 10 Gy/5 fr./1 wks	39 months	8.8%	0.3%	<0.001
Clark *et al.*	857	T≤4 cm	Lumpectory	Conserved breast 40 Gy/16 fr./3 wks Boost 12.5 Gy/5 fr./1 wks	43 months	25.7%	5.5%	<0.0001
Fisher *et al.*	1,265	T≤4 cm	Lumpectory	Conserved breast 50 Gy/25 fr./5 wks	81 months*	39%	10%	<0.001

*: Mean; T: tumor; Quadrantectomy: resection of a quarter of breast; Lumpectomy: local tumor excision

performed). Radiation therapy was performed on the whole breast of the involved side, and 2 Gy dose 5 times a week, for a total dose of 50 Gy of tangential irradiation was undertaken. A total of 10 Gy of boost irradiation was carried out for 325 patients in whom a malignant tumor was found on or within 5 mm from the tumor stump. Tamoxifen and 5-FU (including derivatives) are administered for two years after breast conserving therapy.

The observation period ranged from 2 to 142 months with a mean of 51 months, and 26 patients died of breast cancer, 7 of other diseases, and 2 of suicides. Twenty-nine recurrences within the involved breast, and 92 distant metastatic lesions were observed. There were 29 metastases in bone, 18 in the lung, 29 in supraclavicular lymph nodes or parasternal, and 16 in others. The overall 5-year survival rate, cause-specific survival rate, and disease-free survival rate, and local-recurrence-free survival rate was 97.9%, 98.3%, 88.7%, and 97.6%, respectively.

4. Adverse reactions

Adverse reactions associated with radiation therapy are divided into acute ones and late ones. The former is seen during treatment or within a few weeks from the completion of treatment. The major problem is dermal disorder on the irradiated site. In most cases, erythema or dry desquamation is seen. Moist desquamation with pain is found in a small percentage of patients, but it usually disappears within 2 weeks.

Late complication which occurs within a few months or a few years from the completion of treatment, is more serious. It includes radiation pneumonitis, upper-limb edema, costal fracture, radiation arm pericarditis, radiation myelopothy, and pleurisy. With improved irradiation techniques, their frequency has recently declined and they are clinically almost insignificant except for upper limb edema. Combination of radiation therapy and chemotherapy is known to significantly increase the frequency and severity of adverse events irrespective of whether they are acute or late.

Regarding carcinogenesis caused by radiation therapy, three phase-III clinical trials by WHO, NSABP, and the Milano Cancer Institute found no differences between breast conserving treatment and mastectomy in terms of the frequency of breast cancer on the other breast and secondary cancer (Table 2).

Table 2 Radiation Treatment and Secondary Cancer

	Frequency of breast cancer on the other breast	Frequency of malignant tumor other than breast cancer
Breast conserving therapy		
WHO trial	9%	
NSABP trial	3%	3%
Milano trial	5%	2%
Mastectomy		
WHO trial	9%	
NSABP trial	2%	2%
Milano trial	6%	2%

Postoperative Prophylactic Irradiation for Regional Lymph Nodes

The purpose of this treatment is to reduce recurrence rate of the locoregional (chest wall and supraclavicular and parasternal lymph nodes), leading to the improvement of the survival rate.

1. Radiation therapy

Irradiation methods are different to some degree according to the field to be irradiated. In the U.S. and Europe, the chest wall is irradiated in addition to regional lymph nodes. In this case, tangential irradiation is performed on the chest wall, and anterior single-port irradiation is performed to supraclavicular lymph nodes.

Supraclavicular and parasternal lymph nodes in Japan are the target of prophylactic information. A total dose of 50 Gy, 2 Gy 5 times a week is given.

2. Clinical outcomes

Many clinical trials have shown that postoperative irradiation significantly reduces the locoregional recurrence rate. While some reports, such as that of the Stockholm trial, indicate an improved survival rate, most reports did not show the survival benefit. Our experience showed similar results.

Recent reports have shown that a combination of systemic chemotherapy and prophylactic irradiation resulted in an improved survival rate of premenopausal patients with lymph-node-positive breast cancer. Therefore, postoperative irradiation should be reviewed.

Radiation Therapy for Distant Metastatic Lesions

Distant metastatic lesions of the bone, brain, spinal cord, choroid, skin, and lymph nodes are candidates for radiation therapy. This treatment is not aimed at achieving a cure, but is for a palliative purpose, and the alleviation of symptoms will improve patients' QOL. Therefore, the treatment method should be determined based on the purpose of the treatment, acceptable adverse events, and prognosis for each patient. For example, irradiation for a month is disadvantageous, and no attention should be paid to late changes in a patient with a life expectancy of only a few months.

1. Bone metastasis

Bone metastasis with pain or a high possibility of pathologic fraction is an indication for radiation therapy. Relief of pain is obtained in more than 90% of patients, and persistent effects can be expected in 75–80%. Prophylaxis of pathologic fracture is also significant. In 78% of bone lesions, the improvement is obvious on the x-ray examinations. A total dose of 50 Gy is irradiated in a patient with a life expectancy of over a year. More short-term irradiation should be delivered to a patient with poor prognosis. Various types of fractionation schemes, such as 10 Gy/twice/week, 15–20 Gy/5 times/week, and 30 Gy/10 times/2 weeks, are employed. Any of them shows high effectiveness for pain relief. Irradiation of 30 Gy/10 times/2 weeks is the most commonly used among them.

Conclusion

Radiation therapy is often used in the man-

agement of breast cancer, and contributes to improving QOL and the survival rate. A recent significant progress is its role in breast conserving therapy. A combination of radiation therapy and conservative surgery has achieved equivalent results to mastectomy with fewer functional, cosmetic and mental deterioration.

In the U.S. and Europe, it is reported that prophylactic irradiation to regional lymph nodes and the chest wall following mastectomy for sub-groups of breast cancer, which has been rarely performed for a decade in Japan, shows effectiveness when combined with systemic chemotherapy. Therefore, this role of radiation therapy should be reassessed.

Post-operative Follow-up of Breast Cancer Patients

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Hideo INAJI*, Yoshifumi KOMOIKE, Kazuyoshi MOTOMURA and Hiroki KOYAMA**

** Head, ** President, Department of Surgery,*
Osaka Medical Center for Cancer and Cardiovascular Diseases

Abstract: Breast cancer recurrences are classified according to their sites; (1) local recurrence, (2) recurrence at regional lymph nodes, and (3) distant recurrence. After the breast conservation surgery, recurrence may occur (4) within the breast. Post-operative follow-ups should include physical examination of sites where recurrence is likely to occur and the contralateral breast. Guidelines for breast cancer surveillance recommended by the American Society of Clinical Oncology (ASCO) teach that regular and frequent post-operative imaging tests are not necessary, the clinical findings should be studied, and annual mammography of the preserved and the contralateral breast be performed. We believe, however, that less invasive tests such as chest X-ray, tumor markers, etc. should be conducted routinely while other imaging tests (bone scintigraphy, abdominal computed tomography and ultrasonography) should be given individually. Providing information on recurrences and teaching self-examination of the contralateral breast are also important.

Key words: Breast cancer; Follow-up; Recurrence

Introduction

Breast cancer requires extensive post-operative surveillance. In the early post-operative stage, psychological as well as physical care should not be neglected. Japan has no established guidelines for intervals or modalities of the follow-up tests, and institutions follow the course by considering the actual conditions. This paper discusses the guidelines for post-operative surveillance of breast cancer in the United States, and the current status of and the principles followed by the Osaka Medical Center for Cancer and Cardiovascular Diseases.

Sites and Timings of Breast Cancer Recurrence and Incidence of Second Primary Cancers

Breast cancer recurrences are classified by

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Table 1 Follow-ups of Breast Cancer Patients
—ASCO Guidelines[6] and current practice at Osaka Medical Center for Cancer and Cardiovascular Diseases—

Test	ASCO Guidelines (partially modified)	Osaka Medical Center for Cancer and Cardiovascular Diseases
1. History/eliciting symptoms and physical examination	Every 3–6 mos (0～3 yrs) Every 6–12 mos (3～5 yrs) Every year (5 yrs～)	Every 3 mos (0～2 yrs) Every 6 mos (2～5 yrs) Every year (5～10 yrs)
2. Breast self-examination	Every month	Any time
3. Mammography (contralateral breast, ipsilateral breast)	Every year	As needed
4. Pelvic examination	Every year	As needed
5. Hematology, blood chemistry, tumor marker tests	No regular test needed	At the same interval as 1
6. Chest X-ray	No regular test needed	At the same interval as 1
7. Bone scintigraphy	No regular test needed	As needed
8. Abdominal ultrasonography	No regular test needed	As needed

sites roughly into three; (1) local recurrence (on the chest wall of the diseased breast), (2) recurrence at regional lymph nodes, and (3) recurrence at distant sites. After breast conservation surgery, recurrence uniquely occurs (4) within the ipsilateral breast. Metastases occur at distant organs such as the bone, lung and/or pleura, liver, and brain, but distant metastasis occurs more often in the bone, lung and/or pleura in this order. Although recurrences of breast cancer usually occur within five years as in other cancers, they also occur characteristically at later times. On the other hand, ipsilateral breast tumor recurrence after breast conservation surgery occurs in 1–2% of patients per year rather than at any particular time. The sites where recurrences are likely to occur and the contralateral breast should be monitored in the post-operative follow-ups.

The incidence of breast cancer patients developing cancer of other organs is higher by 30% compared to the general population, and detection is reported rather early following the surgery.[1] Tamoxifen widely used in adjuvant therapy following breast cancer surgery is known to slightly increase the risk of endometrial cancer, but this is not considered a problem in Japan.[2] Care may become necessary in the future since the standard duration of adjuvant tamoxifen is now longer than 2 years (usually 5 years).

Follow-up After Breast Cancer Surgery

Frequent examinations as post-operative surveillance are generally believed to lead to early detection of recurrences and greater benefits to the patients. The theory is, however, disputed,[3] and the view that frequent tests (except mammography) are not necessary seems to prevail overseas. The results of two large-scale randomized trials in Italy showed that early detection of recurrences by frequent tests did not mean longer survivals or improvements in quality of life (QOL).[4,5] These clinical trials compared the overall survival and QOL of the two groups; patients in both groups had physical examination and mammography, while patients in the intensive follow-up group had, in addition, chest X-ray, bone scintigraphy and abdominal ultrasonography every six months. The results showed no inter-group differences.[4,5]

The guidelines for breast cancer surveillance recommended by the American Society of Clinical Oncology (ASCO)[6] do not suggest regular or frequent imaging tests (Table 1). We are somewhat puzzled by the fact that the guidelines do not recommend tumor marker tests. There may be an economic reason in the background, but we believe some tests are still essential in order to maintain an adequate doctor-patient relationship. On the other hand, ASCO

guidelines recommend annual mammography for the contralateral and the ipsilateral breasts (for patients who received breast conservation surgery), which we find rather too frequent.

There are many institutions in Japan that give intensive follow-up tests such as bone scintigraphy. Usually, no problems are encountered even if bone scintigraphy is limited to symptomatic patients. At our institute, we frequently perform non-invasive tests such as chest X-ray and tumor markers, but we have no standards for performing bone scintigraphy or abdominal ultrasonography, which are given when specifically called for (Table 1). It would be reasonable to perform tests on ad hoc basis at adequate intervals according to individual risks for recurrence based on the disease stage and various prognostic factors. As recurrences after 10 years are quite few, we let the patient decide when to visit the clinic for follow-up.

In the case of follow-ups after breast conservation surgery, a special consideration is necessary in detecting recurrences in the breast. Prognosis of the ipsilateral breast tumor recurrence following a conservation surgery is generally favorable except for inflammatory-type local recurrence, and repeated lumpectomy is possible in some cases.[7] Early detection is meaningful as in the case of contralateral breast cancer. It is important to have the patients realize the significance of self-examination of the ipsilateral as well as the contralateral breast as recommended by the ASCO guidelines.

Psychological Support

Now that physicians are naturally expected to tell the patient about the cancer, its stage and the therapeutic policy, follow-up in psychological aspect is gaining importance.

Because of the unique character of the affected organ (breast), the sense of loss suffered by the mastectomy patient is grave and she requires psychological support. With the use of breast-conserving surgery, improvement in QOL is observed. According to the result of a questionnaire survey conducted by a study group of the Ministry of Health & Welfare in Japan, it was confirmed that the sense of well-being was quite high in patients who received breast conservation surgery.[8] To those patients with great psychological burden after mastectomy, breast reconstruction should be recommended.

One problem regarding QOL following breast cancer surgery concerns pregnancy. Recent trend is to regard that there are limited evidences to support the theory that post-operative pregnancy affects prognosis. Therefore, pregnancy may be tolerated in low risk patients who do not need adjuvant therapy. Provided, however, the patient who receive adjuvant therapy should be recommended to use contraceptives for two years following the surgery[9] and for one month after completion of the therapy.

Conclusion

Follow-ups after breast cancer surgery were discussed. Although Japan has no established guidelines yet, the authors believe that non-invasive tests (such as chest X-ray and tumor markers) should be given routinely while other imaging tests should be performed on individual basis by considering individual risks. Offering information on recurrences and importance of self-examination of the ipsilateral and the contralateral breasts (in patients who received the breast conservation surgery) is extremely important.

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Is Sentinel Node Biopsy Practical?
—Benefits and Limitations—

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Shigeru IMOTO[*1], Satoshi EBIHARA[*2] and Noriyuki MORIYAMA[*3]

[*1] *Breast Surgery Division, National Cancer Center Hospital East*
[*2] *Director, National Cancer Center Hospital East*
[*3] *Chief, Diagnostic Radiology Division, National Cancer Center Hospital*

Abstract: Surgical treatment of breast cancer is beginning to undergo a major change with the development of sentinel node biopsy, which identifies the first lymph node to receive a lymphatic flow from the tumor. Sentinel node biopsy has made it possible to dispense with unnecessary lymph node dissection in histologically node-negative breast cancer. In the U.S. and Western European countries, phase III clinical trials are currently underway to assess sentinel node biopsy in comparison with conventional axillary lymph node dissection. At the same time, breast cancer treatment consisting of sentinel node biopsy alone is actually being introduced in early stage breast cancer with no clinical evidence of lymph node metastases. This article describes sentinel node biopsy in breast cancer patients performed in our hospital and discusses its future prospects.

Key words: Breast cancer; Sentinel node biopsy; Lymph node dissection; Minimally invasive surgery

Introduction

Surgical operations such as the excision of tumors and the dissection of the regional lymph nodes laid foundation for the radical operations of solid cancer. Although drug therapy with molecular targets is clinically applied to solid cancer these days, the fact that surgical operations are the principal approach in cancer treatment remains unchanged. However, this established notion has now been greatly challenged. Lymph node dissection is performed to prevent lymphatic metastasis to the entire body. In approximately half of operable solid cancers, however, no histologic metastases are observed in dissected regional lymph nodes. Furthermore, there exist many problems associated with the surgical invasiveness of lymph node dissection, which can trigger post-operative complications and sequelae.

Sentinel lymph nodes (SLN) are defined as the first lymph nodes to receive lymphatic flow

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Table 1 Reagents Used in Sentinel Node Biopsy

Dye	
Generally used in the U.S. and Europe	isosulfan blue
Generally used in Japan	isosulfan blue indigocarmine patent blue indocyanin green
Radioisotopes (All labeled with Technetium-99m)	
Generally used in the U.S. and Europe	sulfur colloid colloidal albumin antimony sulfide
Generally used in Japan	human serum albumin tin colloid phytate

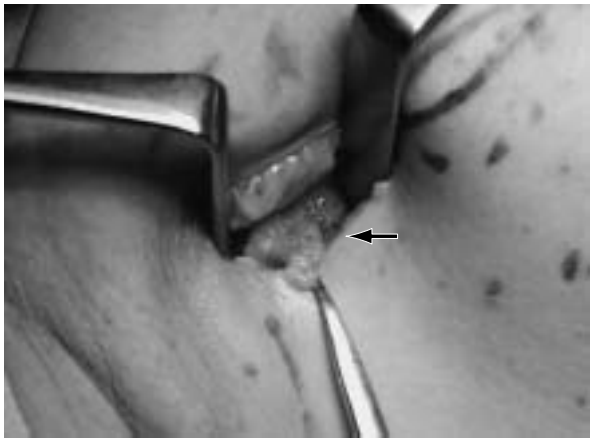

Fig. 1 Dye-guided sentinel node biopsy
A blue-dyed lymph node (arrow) is identified through minimal incision in the axilla, and the presence of metastasis is examined.

from the tumor. No identification of cancer cells metastasizing from the breast in SLN means the absence of metastases in the remaining regional lymph nodes, which implies that the quality of cancer treatment will be maintained even without conventional axillary lymph node dissection. Sentinel node biopsy (SNB) is an approach to identify and biopsy SLN during surgery. The author calls SLN "Mihari" lymph node in Japanese, because it is a lymph node that "keeps an eye on cancer metastasis."

This article describes the current trends and future prospects of SNB in breast cancer.

Descriptions of SNB Techniques

1. Dye method

Dye-guided SNB is a method to identify lymph nodes in the adipose tissue by visually capturing a lymphatic flow from the tumor. While isosulfan blue is commonly used in the U.S. and Western European countries, other dyes are often used in Japan (Table 1). Under general anesthesia, a dye is injected subcutaneously in several sites around the tumor, and the peripheral of the injected sites is massaged in a wrapping motion for a few minutes. Ten minutes later, the axilla is minimally incised to identify blue-stained lymph ducts or nodes (SLN) in the adipose tissue (Fig. 1). The time required from the first skin incision to the identification of SLN is 10 minutes or shorter. Since thorough hemostasis and a clear view of the surgical field are essential in successful dye-guided SNB, experiencing 30 to 50 cases are necessary to master this technique.

2. Lymphoscintigraphy and gamma probe detection

Lymphoscintigraphy and gamma probe detection are methods to identify SLN using radioisotopes (Table 1). These methods require a gamma probe, which is a highly sensitive gamma ray counter. Radioisotopes, administered preoperatively in the peripherals of the tumor, travel through the lymph duct and are accumulated in SLN. Lymphoscintigraphy can detect the possible location and number of SLN by reading marks on the skin that appear under a scinticamera (Fig. 2). Unlike the dye method, if the radioactivity of SLN is high, SLN can be relatively easily identified by using a gamma probe. In the case of low levels of radioactivity in SLN, however, the detection becomes highly

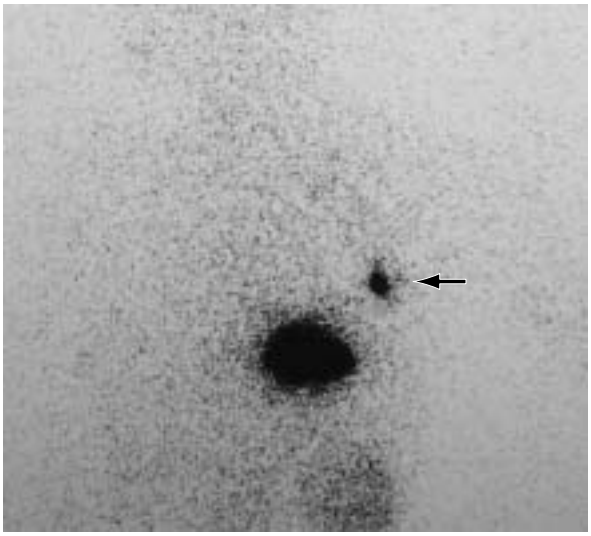

Fig. 2 Visualization of sentinel lymph node by lymphoscintigraphy
Radioisotopes administered in the region of tumor are carried through the lymph duct and accumulated in a sentinel lymph node. The radioisotopes are then detected by a gamma probe.

difficult with the gamma probe alone.

Feasibility Study

Over 100 years have passed since Halsted operation[1] in the 1890s, which marked the beginning of the modern history of surgery for breast cancer, and to this day axillary lymph node dissection continues to be performed. SNB, on the other hand, has seen a remarkable progress over the last 10 years since its first studies in malignant melanoma[2] and breast cancer[3] were reported at the beginning of the 1990s. The presence of SLN in breast cancer has been substantiated, and the SNB methodology can be said to have nearly established (Table 2). Researchers[4–8] all reported the identification rate of over 90% (the success rate for SNB) and accuracy of over 95% (the correspondence in the state of the histologic metastasis between SLN and dissected lymph nodes as a whole). In Japan, SNB began to prevail in the mid-90s and at present a few dozen institutions are introducing the dye or gamma probe method.

Table 2 Sentinel Node Biopsy Feasibility Studies

Reporter	Year	Method	Number of cases	Identification rate	Accuracy	Sensitivity
Giuliano[4]	1997	D	107	93%	100%	100%
Borgstein[5]	1998	R	130	94%	99%	98%
Cox[6]	1998	D+R	466	94%	100%	99%
Veronesi[7]	1999	D	376	99%	96%	93%
Imoto[8]	2000	D+R	56	93%	96%	92%

D: Dye method
R: Gamma probe method with radioisotopes

SNB in Clinical Practice

In our hospital, SNB by the dye method[9] with indigocarmine has been performed since January 1998. Characteristics of lymphoscintigraphy[10] and issues relating to the gamma probe method have also been examined.[8] In the end, on the basis of 200 SNB cases, we established the two-mapping technique[11] applying the dye method and a double tracer technique. Since July 1999, SNB has been performed in clinical practice mainly in clinically node-negative breast cancer (hereafter referred to as "N0 breast cancer"). Of the 314 cases in which SNB was performed, SLN was identified in 310 cases (99%), and axillary lymph node dissection was not performed in 221 cases (70%) with histologically negative SLN. Even in patients treated only with SNB, radiation therapy is introduced concurrently following breast conservation, and to patients with highly malignant breast cancer, chemo-endocrine therapy is recommended. At present, periodical follow-up of the patients are conducted for local and distant recurrences including axillary recurrence. We also consider examining the quality of life of long-term survivors of breast cancer surgery, including sequelae.

Benefits and Limitations

Although SNB has already been applied in clinical settings in some advanced institutions in Japan, many issues remain unsolved. First

and foremost is the prevalence of the SNB technique. While over 1,500 gamma probes are currently in operation in the U.S., the corresponding figure is approximately 50 in Japan. Furthermore, the entire cost of SNB is borne by researchers themselves. In the U.S. and Europe, dyes used in staining lymph ducts and radioisotopes for lymphoscintigraphy are both covered by insurance. Although the dye method is inexpensive and easy to apply, mastering of techniques is essential. Unlike conventional operations involving lymph node dissection, SNB can improve quality of life and suppress health care costs due to minimal surgical invasiveness and reduced hospitalization. Health insurance coverage for SNB that also includes radioisotopes must be in place for SNB to become widespread.

The second problem to be solved is the histological detection of SLN. Conventional hematoxylin-eosin staining complemented by immunohistochemistry or preparation of multiple SLN slices can detect carcinoma foci that were overlooked in at least 10% of SLN. Permanent histologic analysis can sometimes detect micrometastasis of 2 mm or smaller in SLN that could not be identified with intraoperative immediate pathological diagnosis. Effects of these micrometastastic foci on survival prognosis are unknown. The decision whether to perform lymph node dissection in reoperation is also left to each researcher.

The third problem is the effect of SNB itself on survival prognosis. Results from clinical studies in the past[12] revealed that the preventive dissection of axillary lymph nodes in N0 breast cancer did not lead to improvements in survival prognosis. The reasons for this include that, in certain breast cancer cases, the entire body is already affected by bone marrow micrometastases. In short, distant recurrence cannot be prevented by surgical operation alone in high-risk breast cancer cases. Investigation of clinical significance of SNB itself, and examination of effects of cancer cells in SLN or bone marrow on survival prognosis are critical. In the U.S., large-scale clinical trials of SNB in breast cancer are currently underway in about 4,000 and 7,000 clinical cases.

Conclusion

SNB is epoch-making, because it has released patients with histologically node-negative breast cancer from highly invasive total lymphadenectomy, which had been performed for 100 years, and it has given them a body-friendly alternative. Clinical applications of SNB are not just limited to breast cancer or malignant melanoma, and feasibility studies are now being conducted in various cancers including lung cancer, gastrointestinal cancers, gynecological cancers, and head and neck cancers. Although future prospects of SNB in each organ are unknown, it is easily conceivable that the presence of SLN in each organ will be substantiated. In an era when treatment of each disease is becoming more and more individualized as the result of gene analysis, SNB is expected to make substantial contributions to the individualization of cancer treatment with surgical operations.

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Frontier Medicine and Ethical Issues

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Fumimaro TAKAKU

President, Jichi Medical School

Abstract: Genetic medicine and regeneration medicine are described as the frontier medical science of the 21st century. Genetic medicine is further classified into gene diagnosis and gene therapy, and the former is well known to involve various bioethical problems. In this age of post-genomics, as gene polymorphisms related to life-style related diseases such as hypertension, diabetes mellitus and dementia have been elucidated, the society is pressed to take measures for protecting the information and preventing social discrimination based on the information obtained. There have so far been few ethical issues concerning gene therapy, since the therapy addressed diseases that are not easily curable by conventional therapies. However, various issues will arise in the near future when genes are transduced for improving aesthetic aspects or abilities or competence of individuals. Cloning and ES cells are useful in regeneration medicine, and although cloning of human being is forbidden by law in Japan, production and use of human ES cells are recognized under the prescribed guidelines.

Key words: Life-style related diseases; Regeneration medicine; Gene diagnosis; Gene therapy; Cloning of humans; ES cells

Introduction

With rapid advance in medical sciences, new technologies are being introduced to the medical field with accelerated speed. Genetic medicine and regeneration medicine are typical examples of such a trend. This paper focuses on genetic medicine and regeneration medicine, and discusses bioethical issues related to these two subjects.

Genetic Medicine and Bioethics

In genetic medicine, diagnosis, evaluation of efficacy of treatment, and early detection of recurrences are being performed routinely by DNA analysis of patients for some diseases. In this age of post-genomics when analysis of human base sequences have substantially been concluded and the results are about to be applied to medicine, highly competitive studies are being conducted worldwide to detect genetic changes that are related to life-style

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related diseases or adult-onset disorders such as hypertension, diabetes mellitus, and dementia, and to apply the changes to prevention and diagnosis of these diseases.

In the not-so-distant future, DNA screening of individuals will be conducted to find their susceptibilities to specific diseases and to take preventive measures for the life-style related diseases based on the screening results.

As for gene diagnosis, there already exist controversies about justification of gene diagnosis of inseminated eggs, and an ineffectual counseling system for families whose gene screening confirmed the diagnosis of congenital disease. There are a series of diseases that may be diagnosed prior to onset by gene screening such as Huntington's disease, familial amyloidosis, and breast and ovarian cancers with familial predisposition. Gene diagnosis for such diseases presents major challenge worldwide in bioethics regarding individual options for diagnosis, counseling after diagnosis, protection of confidential information, and genetic screening required for purchasing insurance policies.

If susceptibility to life-style related diseases can be identified by DNA testing, the subject population will increase considerably from the limited number of subjects currently being tested for congenital diseases and some tumors. The issue warrants extensive discussions among the general public rather than by medical personnel only as it involves the entire population. If gene diagnosis was to be conducted routinely, these issues of bioethics will constantly arise in the front line of medical care.

As for the gene therapy which was launched in 1990, it is still in the stage of clinical studies. However, there are more than 4,000 subjects in 400 protocols worldwide, and successes are reported regarding researches on some congenital diseases. Compared to other countries, there are very few examples in Japan, but gene therapy on lung cancer, prostate cancer, brain tumor, some congenital diseases and obstructive angiopathy have so far been conducted.

Gene therapy targets patients with intractable diseases that cannot be cured by conventional treatment. In this context, one may say that there are few bioethical issues. However, in view of further diffusion of gene therapy, genes may be used for improving appearances or abilities of individuals, and it may be prudent for us to address such a situation including ethical issues in advance.

Regeneration Medicine

Examples of studies related closely to regeneration medicine include cloning of sheep by Wilmut *et al.* in 1997, and development of human embryonic stem cells (ES cells) in 1998. The former was an epoch-making scientific experiment in that it demonstrated that all DNA segments constituting an individual being are contained in the nucleus of somatic cells of a mature mammalian animal. It led to global discussion on possibilities of cloning a human being and its justifiability. Opinions that advocate prohibition of such cloning prevail worldwide, and Japan enacted "the Law Concerning Regulation of Cloning Technology, etc. for Humans" (commonly known as "Clone Law") in November 2000.

ES cells have been demonstrated to differentiate into various cells such as nerve cells, pancreatic islet cells, myocardial cells and blood cells at the level of mice, and human ES cells were recently demonstrated to successfully differentiate into hemopoietic cells, myocardial cells and pancreatic islet cells. Human ES cells will soon be used in various medical specialties in cell transplantation. Patients and researchers of diabetes mellitus, Parkinson's diseases, Alzheimer's diseases and spinal injuries look upon transplantation of pancreatic β cells or neurocytes derived from ES cells with much expectation.

As is well known, two groups respectively represented by Thomson of University of Wisconsin and Gearhart of Johns Hopkins University have established the human ES cells. The

former produced ES cells from surplus artificially inseminated eggs and the latter from reproductive cells of dead fetuses. As the US Government forbids the use of government research funds for producing human ES cells, these two strains of human ES cells were made with private funds.

Japanese Government published the guideline for preparation and use of human ES cells in September 2001,[1)] and European countries such as UK and Switzerland recognize preparation and use. On the other hand, the government funds are not available for researches of human ES cells in the United States as mentioned above because of strong oppositions from Catholic churches, etc., because human ES cell production entails destruction of human embryos.

However, strong demands from researchers and patient groups for development of human ES cells prompted President Bush to publish his government's policy in August 2001 of allowing the use of government funds only for researches using already existing human ES cells. This however means that the use of government research subsidies for new human ES cells is prohibited, and caused scientists to strongly oppose it. UK recognizes not only production of human ES cells but also preparation of human clone embryos by taking out the nucleus from the patient's somatic cells and inserting the nucleus into denucleated donated eggs. Some Americans voiced concern for consequent delays in ES cell researches and regeneration medicine as capable researchers immigrate to UK.

As for the use of the human ES cells for cell transplantation, there still remain many technical problems that need to be overcome. But considering the current speed of researches and developments, it is highly probable that they will be applied to clinical medicine in the near future.

Another technology, which may be successfully applied clinically to regeneration medicine, is the use of somatic stem cells. It is known that in addition to hemopoietic stem cells that may differentiate into various cells, somatic stem cells are present in the bone marrow of higher mammals including humans. Since transplantation of somatic stem cells uses stem cells of the patient, there are fewer ethical problems compared to human ES cells.

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