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, post-operative 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
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 treatment.

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-areola 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
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. According to the clinical classification, there were 49 Tis, 70, 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
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 myelopathy, 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).
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 fracture 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 a life expectancy of a year. 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.

Table 2 Radiation Treatment and Secondary Cancer

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<th>Frequency of breast cancer on the other breast</th>
<th>Frequency of malignant tumor other than breast cancer</th>
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<tr>
<td>Breast conserving therapy</td>
<td>WHO trial 9%</td>
<td>3%</td>
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<td></td>
<td>NSABP trial 3%</td>
<td>3%</td>
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<td></td>
<td>Milano trial 5%</td>
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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.

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.