Panel Discussion

Analysis of Ipsilateral Breast Tumor Recurrences after Breast-conserving Treatment Based on The Classification of True Recurrences and New Primary Tumors


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**Background:** Ipsilateral breast tumor recurrences (IBTR) after breast-conserving treatment include two different entities: true recurrence (TR) thought to occur when residual cancer cells grow gradually to detectable size and new primary (NP) thought to be de novo cancer independently arising in the preserved breast. The patients with ipsilateral breast tumor recurrence (IBTR) are potentially at high risk for subsequent distant metastasis, but many studies do not distinguish between these types of recurrence. The aim of this study is to clarify the biological difference between TR and NP, and to show the clinical significance of classifying IBTR into these two types of recurrence.

**Patients and Method:** A total of 172 patients with IBTR after breast-conserving therapy from the cohort of a long-term large scale study (Research of cancer treatment from the Ministry of Health, Labor and Welfare of Japan (no.13-9)) were analyzed. We classified IBTRs as TR or NP based on tumor location and pathological findings. The characteristics of the primary tumors of TR and NP were compared. Survival rates and risk factors of each type of IBTR were examined by the Kaplan-Meier method. The results of salvage surgery were also analyzed.

**Results:** Of the 172 patients, 135 patients were classified as TR and 26 as NP. Eleven cases could not be categorized. The primary tumor of TR was characterized by a high rate of lymph node metastasis (37.8%) and short disease-free interval (mean DFI; 46.6 months) while that of NP showed a rather low lymph node positivity (8.7%) and longer DFI (62.1 months). The risk factors for TR were young age, positive surgical margin, omission of irradiation and positive lymph node metastasis. Those for NP were young age, omission of irradiation and contralateral breast cancer after the primary operation. The 5-year survival rates after IBTR were 71.0% in TR and 94.7% in NP (p = 0.022). Salvage operation was performed in 136 IBTRs. Eighty-one patients underwent salvage mastectomy and 55 patients underwent repeat lumpectomy. Five-year survival rates after salvage operation were 75.7% for mastectomy and 84.2% for lumpectomy. Twenty percent of patients who underwent repeat lumpectomy developed secondary local relapse within 5 years after salvage treatment. The risk factors for secondary local relapse were analyzed. Limited to cases of IBTR which received radiation therapy after the primary operation, NP was the only factor influencing secondary local relapse by univariate analysis.

**Conclusions:** TR and NP show clinically quite different features; time to occurrence, characteristics of the original tumor, prognosis and risk factor profile for IBTR were all different. Classifying IBTR as TR or NP can provide clinically significant data for the management of IBTR.

A number of prospective and retrospective studies have shown that breast-conserving therapy is standard of care for Stages I and II breast cancer. Twenty-year follow-up data from the NSABP B-06 and Milan trials showed equal survival between mastectomy and conservative surgery. Those same results also showed ipsilateral breast tumor recurrence (IBTR) over 10 years after primary operation even though the rate was under 1% per year. The increasing number of women opting for breast conservation means that IBTR is becoming a significant clinical issue.

The IBTR rate is about 5% to 10% at 5 years and 10% to 15% at 10 years. There is an increasing risk of relapse in the first few years after primary operation which levels off after approximately 5 years. The average interval to IBTR ranges 34 to 60 months. Most studies have found that omission of postoperative irradiation, resection margin status, young age, an extensive intraductal component (EIC) and lymphatic vessel invasion correlate with a higher risk of IBTR. The overall survival after IBTR averages about 74% at 5 years and 65% at 10 years and the disease-free survival averages 60% at 5 years and 57% at 10 years. These survival rates are better than those of patients with chest wall recurrence after mastectomy. It is, however, often reported that IBTR is actually one of the strongest prognostic variables available to predict distant metastases or death from breast cancer. Most studies have reported that the relative risk of distant metastases with IBTR ranges from three- to five-fold. The interval between initial treatment and local relapse, nodal status at the time of initial treatment and initial tumor size were reported to correlate with subsequent distant metastasis. Whether IBTR is a determinant or indicator of distant metastases is now unclear. Currently, the standard treatment of IBTR is salvage mastectomy, which has provided locoregional control in 90% of patients. The use of repeat lumpectomy as an alternative to mastectomy, chemotherapy, endocrine therapy and additional partial irradiation remain controversial. The optimal systemic therapy after IBTR is also unknown. Thus the issues arising from IBTR such as biological behavior and treatment options are expected to be clear.

One of the concerns regarding IBTR is whether it is a recurrent tumor or a second primary tumor. It recently became clear that a significant portion of patients with IBTR actually have new primary tumors. In considering IBTR, it is worth to note that IBTR may represent two distinct entities. Veronesi et al. related in their report that true recurrences (TR) were cases consistent with the regrowth of malignant cells not removed by surgery or not killed by radiotherapy. Alternatively, new primary tumors were de novo cases of malignancies arising from mammary epithelial cells of residual breast tissue. Some studies suggested that NP recurrence had a longer mean time to IBTR, was more frequent with young patients, more likely to occur in a different quadrant from the initial tumor and were associated with improved survival. The complicated behavior of IBTR may be related to the fact that the patient population represents these two distinct entities. The location of the first and secondary tumor, as Recht et al. and most other investigators reported, was used in classifying TR/NP. Histological subtypes and time to relapse were also used. The presence of carcinoma in situ, a different histologic type, or better differentiation of the second cancer may help in identifying independent tumors recently, some molecular techniques such as DNA fingerprinting, loss of heterozygosity (LOH) pattern or allelic imbalances profile have been used to distinguish NP from TR, but the classification rules are not standardized yet.

We collected information on Japanese women who had received breast-conserving treatment with the support of the Ministry of Health, Labor and Welfare of Japan. The long-term follow-up results will be described elsewhere. In the current study, we tentatively classified IBTR as TR or NP, and the characteristics, prognosis and risk factors were compared. Also the results of salvage surgical treatment were discussed.