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Original article

Ipsilateral breast tumor relapse after breast conserving surgery in women with breast cancer

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ABSTRACT

Ipsilateral breast tumor relapse (IBTR) is a potentially a significant problem after breast conserving surgery (BCS). With a median follow-up period of 64.7 months, IBTR occurred as a first relapse in 67 (3.0%) of a total of 2243 patients and distant recurrence occurred in 167 (7.4%). A positive surgical margin and the omission of radiotherapy (RT) were independently associated with IBTR. The five-year cumulative IBTR rates were 5.1% in patients with positive margins and 2.0% in the patients with negative margins. The five-year cumulative IBTR rates were 1.8% in patients with RT and 8.1% in patients without RT. IBTR was independently associated with distant-recurrence-free survival rates as well as age, nodal metastasis, lymphovascular invasion and progesterone receptor status. The five-year distant-recurrence-free survival rates were 81.9% in patients with IBTR and 93.2% in patients without IBTR. In order to prevent IBTR, a negative margin and the administration of RT are therefore considered to be important in patients who undergo BCS.

Introduction

Breast conserving surgery (BCS) is the standard method of surgery for women with early-stage breast cancer. Recently BCS has been the most common surgical method in Japan and it is estimated to be performed in about 60% of all the cases of breast cancer surgery.[1] BCS was started in the 1970s in Europe and America and there was no difference in overall survival in comparison with a modified radical mastectomy over a long period of time.[2,3] A meta-analyses of randomized controlled trials by the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) showed that the local recurrence rate and 15-year-overall survival rate after BCS accompanied by radiation therapy (RT) were similar to those after a mastectomy alone.[4] RT to the whole breast after BCS significantly reduced the incidence of ipsilateral breast tumor relapse (IBTR; 2,3,5–8). Therefore, the standard strategy is that BCS is followed by RT. RT is also effective in preventing local recurrence after a mastectomy and as the result, it can improve overall survival.[9,10] In addition to RT, systemic adjuvant therapy significantly reduces the incidence of IBTR.[11–13] Recently, some studies have reported a negative surgical margin and the use of systemic adjuvant therapy with or without RT improved local control rates after BCS.[12,14] Therefore systemic therapy, as well as RT, may play a significant role in preventing IBTR after breast conserving therapy in breast cancer patients.

IBTR is a potentially a significant problem that always raises the question of whether IBTR would have occurred if a mastectomy had been performed. The results of the EBCTCG meta-analyses and other studies suggest that IBTR is associated with worse overall survival rates.[15–19] However, it is debatable whether IBTR is an indicator of subsequent distant metastases or a cause of it.[20–25] Regardless of this, IBTR should be avoided and for that purpose it is necessary to elucidate the risk factors for IBTR.

There are several known risk factors of IBTR. The surgical margin status is a major factor affecting IBTR; a positive surgical margin is significantly correlated with a higher incidence of IBTR.[26–30] However, a positive surgical margin is not clearly defined.[26,28,30] Other risk factors for IBTR are reported to be patient age, tumor size, histological grade, nodal status, hormone receptor status and lymphovascular invasion (LVI).[13,31–35] These are also the risk factors of distant recurrence.[16,21,23]

BCS began to be performed in 1987 in the Saitama Cancer Center. Over the two decades since the beginning of BCS, the rate of BCS among all surgery cases has recently increased up to over 80%.

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The number of BCS cases exceeded 3000 in December 2007. The present study retrospectively analyzed the risk factors for IBTR and also for distant recurrence separately in patients treated at a single institution. In addition, in order to clarify whether IBTR is an indicator of subsequent distant metastases or the cause of it, this study determined whether IBTR was a significant risk factor for distant recurrence and the annual rates of distant recurrence after BCS in patients who experienced IBTR. If the annual rates of distant recurrence were the same between these patients, IBTR might just be an indicator, not the cause for distant recurrence.

Materials and methods

Patients

All of the women with breast cancer who underwent surgery at the Saitama Cancer Center have been included in a database since 1975. BCS began to be performed in 1987 and a total of 3623 breast cancer cases treated with BCS were recorded by December 2007. In this study, a consecutive series of women with primary unilateral breast cancer who were treated with BCS from January 1987 to December 2005, treated without neoadjuvant therapy were retrieved from the database. A total of 2243 women were included in this study (Table 1); their mean age was 53.2 years (range, 21–88).

Surgical therapy

Patients who were initially treated with BCS underwent a quadrantectomy. From the latter half of 1990s, patients treated with BCS underwent tumor resection with grossly normal tissue margins of 1–2 cm, generally down to the fascia. When the tumor was close to skin, the skin overlying the tumor was resected. Axillary lymph node dissection (ALND) was not performed when the sentinel lymph nodes were found to be tumor-free since 1999.[36]

Pathological assessment

The volume excised by BCS depended on the size of the tumor; whereas, it become smaller as the standard procedure evolved from a quadrantectomy to a lumpectomy over the past 20 years. The excised breast tissue was fixed with 10% formalin and then sliced vertically along the axis from the primary tumor to the nipple at 5 mm intervals. Paraffin embedded sections were made from all slices of the excised breast tissue. A positive margin was defined as cancer cells which were present within 5 mm from each cut surface except on an anterior or posterior surface.

Adjuvant therapy

RT to the whole breast with a dose of 50 Gy, while in addition the irradiation was boosted with a dose of 10 Gy applied to the tumor bed in cases with a positive surgical margin was given to a total of 1857 (82.8%) patients.

Adjuvant endocrine therapy and chemotherapy were administered in 1427 (63.6%) and 591 (26.3%) patients, respectively.

Risk factors for IBTR and distant metastases

The IBTR was defined as all recurrences only in the breast but not in the axilla. The clinical and pathological features at the primary surgery, such as age, tumor size, ALND, pathological nodal metastases, LVI, estrogen receptor (ER), progesterone receptor (PR), RT, adjuvant endocrine therapy and adjuvant chemotherapy were analyzed for any correlation with IBTR and distant recurrence. LVI was classified into 0, 1+, 2+ and 3+ by a pathologist (M.K.) and 0 and 1+ were integrated into negative LVI and 2+ and 3+ were integrated into positive LVI in this study.[37] The positive ER and positive PR were determined to be $\geq$13 fmol/mg protein and $\geq$10 fmol/mg protein, respectively, by enzyme immunoassay until 2003 and these were $\geq$10% positive cells by immunohistochemistry, thereafter.[38]

IBTR and distant metastases

IRTR was statistically analyzed as a risk factor for distant recurrence as well as other risk factors. The annual rates of distant recurrence after the primary surgery were calculated separately in patients who did and did not experience IBTR.

Statistical methods

The Kaplan–Meier method was used for calculating survival. The log-rank test was used for determining the statistical significance. An analysis of variance was used for determining the difference in the time periods between patients who did and did not experience IBTR. Univariate and multivariate analyses using the Cox proportional hazard regression model were used for evaluating risk factors

Table 1
Clinicopathological characteristics.

Characteristics		No. of patients
Age	<35	91
	≥35	2152
Menopausal status	Pre	1072
	Post	1171
Tumor size	Tis	167
	T1	875
	T2	1122
	T3	62
	T4	17
ALND	No	994
	Yes	1249
LN metastases	Negative	1472
	1–3	551
	≥4	195
	Unknown	25
LVI	−	1970
	+	243
	Unknown	30
Margin	−	1402
	+	708
	Uncertain	133
ER	+	1458
	−	688
	Unknown	97
PR	+	1362
	−	780
	Unknown	101
RT	+	1857
	−	386
Adjuvant ET	+	1427
	−	816
Adjuvant CT	+	591
	−	1652

ALND, axillary lymph node dissection; LN, lymph node; LVI, lymphovascular invasion; ER, estrogen receptor; PR, progesteron receptor; RT, radiation therapyl; ET, endocrine therapy; CT, chemotherapy.