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Breast-conserving surgery without radiation in elderly women with early breast cancer

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ABSTRACT

Background and objectives: Irradiation after breast-conserving surgery (BCS) decreases the incidence of ipsilateral breast tumor recurrence (IBTR) and breast cancer-related death. However, daily radiation treatments are burdensome to elderly patients, whose risk of IBTR is relatively low. Since 2001, we have offered BCS without radiation to patients meeting our selection criteria. This study assessed the prognosis of the patients who chose this option.

Methods: Between 2001 and 2014, 203 patients met the selection criteria: aged ≥60 years; pathologically node-negative, hormone-positive breast cancer; a negative surgical margin; and no lymphovascular invasion. Among these patients, 84 and 119 underwent BCS with or without radiation, respectively. IBTR, overall survival (OS), and breast cancer-specific survival (BCSS) were evaluated.

Results: The median follow-up duration was 6.2 years. There were no significant differences in tumor size or the number of patients with adjuvant therapy between the groups. The 5-year IBTR rates were 0.9% and 1.6% in the non-irradiated and irradiated groups, respectively ($p = 0.308$). The 5-year OS rates were 94.1% and 98.7% ($p = 0.391$). Similarly, the 5-year BCSS rates were 97.2% and 98.7% ($p = 0.812$).

Conclusion: It is suggested that the omission of irradiation could be an option for elderly breast cancer patients who satisfy our criteria.

1. Introduction

Whole-breast irradiation after breast-conserving surgery (BCS) has been shown to reduce the risk of ipsilateral breast tumor recurrence (IBTR) [1–5] and breast cancer-related death [1]. However, most patients with early-stage breast cancer do not relapse, even in the absence of radiation. Moreover, radiotherapy requires daily hospital attendance, which can be challenging for elderly patients, and the risk of IBTR in elderly patients is low. Veronesi reported a randomized trial in 1993. Subgroup analysis of this trial suggested that there was no significant difference in overall survival (OS) between irradiated and non-irradiated elderly women (≥55 years of age) [6]. Since 1994 to 1999, a randomized control trial (CALGB9343) was conducted and indicated that there was no significant difference in OS between irradiated and non-irradiated elderly women (≥70 years of age) with hormone-positive breast cancer [4,5].

We allowed elderly breast cancer patients to forgo radiation (a standard treatment at the time) if daily visits to our hospital were problematic and specific conditions were met since 1994. Our retrospective analysis showed that the IBTR rate in these patients was relatively low. Consequently, since September 2001, we have offered patients the option of BCS without radiation if they were aged ≥60 years and had pathologically-node negative, hormone-positive breast cancer and a negative surgical margin, with no lymphovascular invasion. Herein we retrospectively assessed the prognosis of patients age 60 years or older satisfying these criteria. A negative margin was defined as a tumor-free margin ≥5 mm.

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2. Patients and methods

2.1. Patients

A total of 1105 patients with primary breast cancer underwent BCS at Tokyo Women's Medical University Medical Center East between September 2001 and December 2014. Of those, 203 patients satisfied the following criteria: age ≥60 years; pathologically node-negative, hormone-positive breast cancer; a negative surgical margin; and no lymphovascular invasion. We allowed patients who met above the criteria to select treatment with or without radiation. The number of patients in the irradiated and non-irradiated groups was 84 and 119, respectively.

2.2. Breast conserving surgery (BCS)

The indication for BCS was Tis–T2 (tumor size up to 3 cm) and excluded multiple tumors. The primary tumor was surgically excised, with a 1-cm margin of normal tissue (only nipple side, 2-cm margin). A negative surgical margin was histologically defined as a tumor-free margin ≥5 mm. Patients with positive surgical margins underwent additional resection to achieve negative margins.

2.3. Radiotherapy

The whole breast was usually irradiated with 50 Gy in 25 fractions during a 5-week period. A boost to the tumor bed (10 Gy in 5 fractions or 9 Gy in 3 fractions) was administered at the discretion of the radiation oncologist.

2.4. Adjuvant therapy

Almost all patients received tamoxifen (20 mg/day) or an aromatase inhibitor (2.5 mg/day letrozole, 1 mg/day anastrozole, or 25 mg/day exemestane) after BCS as adjuvant therapy. A few patients received an anthracycline-based combination regimen, a taxane-based combination regimen, or tegafur/uracil (300 mg/m^2 per day orally for 2 years). The anthracycline-based combination regimen consisted of 4 cycles of EC (epirubicin 90 mg/m^2, cyclophosphamide 600 mg/m^2, q3w). In some instances, it was followed by 12 cycles of paclitaxel (80 mg/m^2 per week). The taxane-based combination regimen consisted of 4 cycles of docetaxel (75 mg/m^2) and cyclophosphamide (600 mg/m^2, q3w).

2.5. Evaluation of clinicopathological factors

The following data were collected from the patients' medical records and pathological reports: age, T, N, adjuvant therapy, IBTR, OS, breast cancer-specific survival (BCSS), surgical margin, lymph node metastasis, lymphovascular invasion, and biomarker expression. Pretreatment images were used for T and N staging, which was done in accordance with the Union for International Cancer Control TNM classification system [7]. Pathological factors were assessed using surgical specimens. Positive reactions for estrogen receptor and progesterone receptor were defined as those showing nuclear staining in ≥10% of the cancer cells.

2.6. Statistical analyses

JMP Pro Ver.11 software (SAS Institute Inc., Cary, NC, USA) was used for statistical analysis. The χ^2 test was used to determine significant differences between irradiation and clinicopathological factors and irradiation and IBTR. Cumulative IBTR, BCSS, and OS rates were determined using Kaplan-Meier plots and the log-rank test.

Table 1
Patient characteristics.

Characteristic	All (n = 203)	Non-irradiated (n = 119)	Irradiated (n = 84)	p-value
Median follow-up time(y)	6.2	6.1	6.3	0.72
Age, median (range)	69 (60–87)	72 (60–87)	65 (60–80)	< 0.0001
T factor				
Tis	37 (18.2%)	24 (20.2%)	13 (15.5%)	0.33
T1	128 (63.1)	70 (58.8)	58 (69.0)	
T2	38 (18.7)	25 (21.0)	13 (15.5)	
Pathological T				
Tis	37 (18.2)	24 (20.2)	13 (15.5)	0.70
T1	116 (57.1)	68 (57.1)	48 (57.1)	
T2	51(25.1)	27 (22.7)	23 (27.4)	
Pathological stage				
0	37 (18.2)	24 (20.2)	13 (15.5)	0.70
I	116 (57.1)	68 (57.1)	48 (57.1)	
IIA	51 (25.1)	27 (22.7)	23 (27.4)	
ER(+), PgR(+)	162 (79.8)	93 (78.2)	69 (82.1)	0.48
ER(+), PgR(−)	41 (20.2)	26 (21.8)	15 (17.9)	
HER2				
positive	10 (4.9)	6 (5.0)	4 (4.8)	0.17
negative	193 (95.1)	113 (95.0)	80 (95.2)	
Hormone therapy				
aromatase inhibitor	162 (79.8)	91 (76.5)	71 (84.5)	0.24
tamoxifen	29 (14.3)	21 (17.6)	8 (9.5)	
no	12 (5.9)	6 (5.9)	5 (6.0)	
Chemotherapy				
yes	13 (6.4)	6 (5.9)	7 (8.3)	0.34
no	190 (93.6)	113 (94.1)	77 (91.7)	
Additional resection				
yes	15 (7.4)	7 (5.9)	8 (9.5)	0.33
no	188 (92.6)	112 (94.1)	76 (90.5)	

ER: estrogen receptor, PgR: progesterone receptor. Median follow-up times and ages are presented in years. All other variables are described in terms of number of patients.

2.7. Ethical statement

This study was approved by the ethical committee of the Tokyo Women's Medical University.

3. Results

The median age at the time of surgery was 65 years (range, 60–80 years) in the irradiated group and 72 years (range, 60–87 years) in the non-irradiated group ($p < 0.001$) (Table 1). There were no significant differences in tumor size or the number of patients with adjuvant chemotherapy between the groups. The median follow-up duration was 6.2 years. The rates of patients treated with aromatase inhibitor were 84.5% vs. 76.5% in the irradiated and non-irradiated groups. Those with tamoxifen were 9.5% vs. 17.6%, respectively. Duration of endocrine therapy was almost 5 years except for recurrent cases. Patients who extended endocrine therapy more than 5 years were not included.

IBTR was observed in 5 (4.2%) patients in the non-irradiated group and 1 (1.2%) patient in the irradiated group ($p = 0.187$) (Table 2). The cumulative IBTR rate was 0.9% and 1.6% at 5 years and 4.8% and 1.6% at 10 years in the non-irradiated and irradiated groups, respectively ($p = 0.308$) (Fig. 1). The BCSS rate was 97.2% and 100% at 5 years and 95.4% and 96.2% at 10 years in the non-irradiated and irradiated groups, respectively ($p = 0.812$) (Fig. 2a). The OS rate was 94.1% and 98.7% at 5 years and 90.1% and 94.9% at 10 years in the non-irradiated

Table 2
Incidence of IBTR.

	All	Non-irradiated	Irradiated	p-value
IBTR	6 (3.0%)	5/119	1/84	0.187

IBTR: ipsilateral breast tumor recurrence.

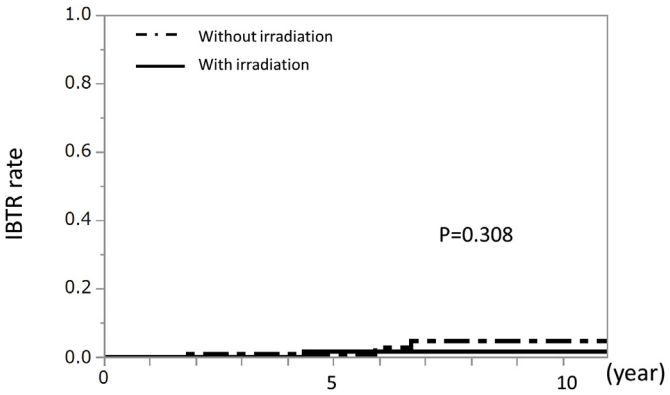

Fig. 1. Kaplan-Meier plots showing cumulative ipsilateral breast tumor recurrence (IBTR) rates. The 5-year IBTR rates were 0.9% and 1.6%, and the 10-year IBTR rates were 4.8% and 1.6%, in the non-irradiated and irradiated groups, respectively (p = 0.308).

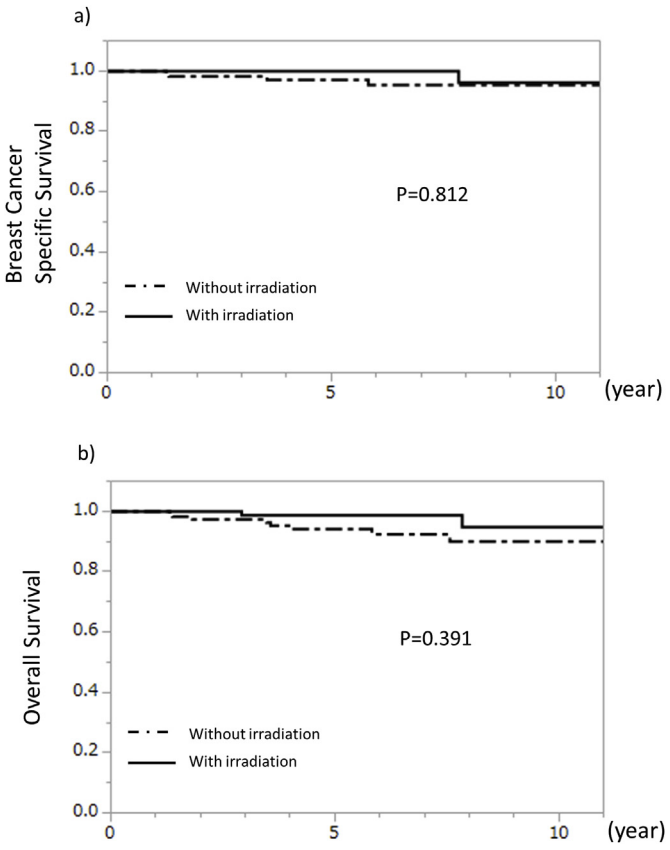

Fig. 2. Kaplan-Meier plots showing breast cancer-specific survival (BCSS) and overall survival (OS) rates a) The 5-year BCSS rates were 97.2% and 100%, and the 10-year BCSS rates were 95.4% and 96.2%, in the non-irradiated and irradiated groups, respectively (p = 0.812). b) The 5-year OS rates were 94.1% and 98.7%, and the 10-year OS rates were 90.1% and 94.9%, in the non-irradiated and irradiated groups, respectively (p = 0.391).

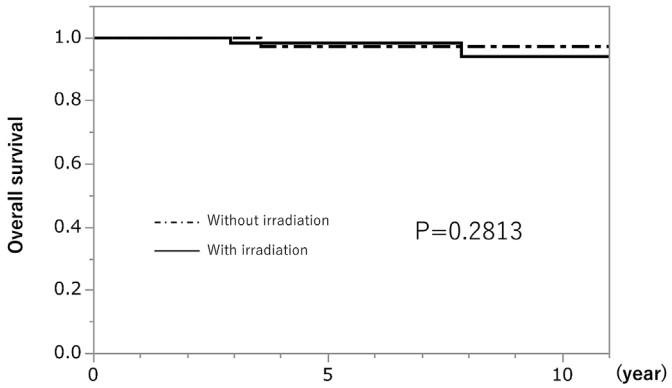

Fig. 3. Kaplan-Meier plots showing overall survival (OS) rates among patients age between 60 and 69. The 5-year OS rates were 97.3% and 98.4%, and the 10-year OS rates were 97.3% and 94.1%, in the non-irradiated and irradiated groups, respectively (p = 0.2813).

and irradiated groups, respectively (p = 0.391) (Fig. 2b). Furthermore, among patients age between 60 and 69, the OS rate was 97.3% at 10 years in the non-irradiated group and 94.1% in the irradiated group (p = 0.2813) (Fig. 3). Recurrent tumors were removed in all cases. Distant metastasis and breast cancer-specific death after IBTR were not observed during the study period.

4. Discussion

A meta-analysis by the Early Breast Cancer Trialists' Collaborative Group in 2005 meta-analysis showed that radiation decreased the incidence of IBTR [1]. However, the rate of IBTR is relatively small in low-risk patients such as elderly woman with low-grade breast cancer. Hence, radiotherapy may represent overtreatment in such patients [8,9]. There are two reasons why there are few effects of irradiation in elderly women. First, multifocal cancers in the ipsilateral breast will be less likely to coexist in elderly women. Second, death caused by other disease increases in elderly women, and some women died before recurrence would be recognized.

We previously identified 2 risk factors for IBTR in non-irradiated breast cancer patients treated at our hospital before August 2001: age < 60 years and a positive surgical margin. Furthermore, hormone-negative status and lymphovascular invasion tended to increase IBTR risk. Beginning in September 2001, we offered BCS without radiation to patients who satisfied the following criteria: age ≥60 years; pathologically node-negative, hormone-receptor positive breast cancer; a negative surgical margin; and no lymphovascular invasion. The present study shows that IBTR, BCSS, and OS rates do not differ significantly between radiated and non-irradiated patients meeting these criteria. Hence, it suggests that BCS without radiation is a valid treatment option for these patients.

In several studies a low-risk group was allowed to treat without irradiation because there were no significant differences in OS rates between irradiated and non-irradiated breast cancer patients [4,5,8–12]. On the other hand, many of them showed significant differences in IBTR rates [4,5,10]. The IBTR rate for non-irradiated patients was lower in our study than other studies [4,5,10]; this may reflect differences in patient selection criteria and the definition of a negative surgical margin. The selection criteria in our study were more restrictive than those in previous studies: T1, hormone-positive status, and tamoxifen administration in the CALGB 9394 study [4,5], and tumor size < 3 cm, node-negative and hormone-positive status, and negative surgical margins in the PRIME II study [10]. The cumulative 5-year IBTR rates in our study, the CALGB 9394 study, and the PRIME II study were 0.9% 4.0%, and 4.1%, respectively [4,5,10]. Hence, the IBTR rate can be reduced by limiting to the patients whose risk was low

according to our selection criteria.

In our study, we defined a negative surgical margin as a tumor-free margin of ≥5 mm [13]. It was defined as the absence of tumor at the inked pathological margins in the CALGB 9349 study [4,5] and as a tumor-free margin ≥1 mm in the PRIME II study [10]. Hence, our negative surgical margin is wider than those in the other studies. Although not statistically significant, the odds of local recurrence tended to decrease as the width of the negative margin increased in the meta-analysis by Houssami et al. [14]: the odds ratios for local recurrence were 1.0, 0.95, and 0.65 for negative surgical margins of 1 mm, 2 mm, and 5 mm, respectively [14]. Therefore, the larger surgical margins in our study may explain at least in part our lower IBTR rate.

IBTR is, of course, not the only indicator of treatment efficacy. Like IBTR rates, OS and BCSS rates were also statistically similar in the irradiated and non-irradiated groups in our study.

Treatment selections for elderly women with breast cancer should be made carefully using established criteria to guarantee safety and avoid overtreatment. Allowing elderly patients to forgo unnecessary radiotherapy reduces their medical expenses, which are rising yearly, and alleviates the burden of daily hospital attendance.

Our study had 3 main limitations. First, it was a retrospective study. Second, because we did not randomize the patients, selection bias by the attending physician may have occurred. In fact, patients were older in the non-irradiated vs. irradiated group. Third, the follow-up period was short and therefore may have been insufficient for estimating prognosis at 10 years. Prospective non-inferiority trials assessing the outcomes of elderly patients receiving BCS without radiation are needed.

In conclusion, there were no significant differences in IBTR, BCSS and OS rates in irradiated and non-irradiated breast cancer patients who fulfilled our criteria. Overtreatment imposes unnecessary costs, risks, and burdens on patients, and our study shows that BCS without radiation is an acceptable treatment option for elderly patients with early breast cancer.

Disclosure

All authors declare that they have no conflict of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.suronc.2019.08.008.

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