

Sentinel-Node-Driven Personalized Radiation Techniques Ranging from Partial Breast Irradiation to Regional Nodal Radiation after Breast-Conserving Surgery*

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ABSTRACT

Background: Breast-conserving surgery (BCS) followed by whole breast irradiation (WBI) has become the standard of care for treating patients with early-stage breast cancer. Recently, various radiation techniques followed by BCS have been reported. We have been investigating “personalized radiotherapy after BCS” ranging from accelerated partial breast irradiation (APBI) to WBI with regional nodal irradiation (RNI) based on the axillary node status. In this study, we compared different cohorts that received personalized radiotherapy. **Method:** Of 317 consecutive patients who underwent BCS followed by radiotherapy since November 2007, 187 who received APBI and 122 who received WBI were analyzed. **Results:** The local-only recurrence rate was 1.1% in the APBI group and 3.3% in the WBI group, and the regional-only recurrence rate was 1.1% for APBI and 0.8% for WBI. **Conclusions:** The clinical efficacy of APBI for local control after BCS was comparable to that of WBI ± RNI. Although this study was based on a small number of patients with a short follow-up period, the feasibility of breast-conserving therapy using multicatheter brachytherapy to achieve acceptable clinical outcomes was demonstrated.

Keywords: Breast Cancer; Personalized Radiotherapy; Sentinel Node; Partial Breast Irradiation; Regional Nodal Radiation

1. Introduction

Breast-conserving surgery (BCS) followed by whole breast irradiation (WBI) is reportedly as effective as mastectomy and has now become the standard of care for treating patients with early-stage breast cancer [1,2]. Although the Oxford meta-analysis demonstrated not only a significant reduction of local recurrence but also an overall survival benefit with adjuvant breast radiation therapy after BCS [3,4], 15% - 30% of patients who undergo BCS refuse WBI [5-10]. The latter may be caused by potential factors, including severe and long-term adverse

events, such as rib fracture, lung injury, and late cardiovascular toxicity, and by long-term daily visits to radiation institutions for at least 5 - 6 weeks. However, no subset of patients who should forego radiation therapy after BCS has been identified [11-13] and local recurrence after BCS with WBI is most likely to occur in the vicinity of the lumpectomy site [14-17]. Considering the above, the efficacy and feasibility of accelerated partial breast irradiation (APBI) as an alternative to WBI have been evaluated in many Phases II and III studies [18-22].

In general, these rapid advances in APBI radiation therapy have been introduced for patients for whom the absence of positive nodes has been confirmed by sentinel-node (SN) biopsy (SNB), and the addition of regional nodal radiation (RNI) to WBI is recommended for pa-

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tients with ≥ 4 positive nodes confirmed by axillary lymph node dissection (ALND). Although the National Cancer Institute of Canada Clinical Trials Group (NCIC CTG) MA.20 trial provided evidence that selected patients with 1 - 3 positive nodes benefit from RNI [23], the number of positive nodes from ALND could still provide important information with regard to several different approaches of radiotherapy. Recently, the American College of Surgeons Oncology Group trial (ACOSOG) Z0011 [24] and the European Organisation for Research and Treatment of Cancer (EORTC) 10981-22023 After Mapping of the Axilla: Radiotherapy or Surgery (AMAROS) trial [25] have shown that both ALND and radiotherapy without ALND provide excellent regional control for SN-positive patients. However, there are several issues such as indications for SNB in which ALND may be omitted and the optimal radiation technique for axilla and systemic treatment after surgery.

Patients who undergo BCS generally receive WBI at our institution; however, we have introduced the concept of “personalized radiation therapy after BCS” to deliver radiation therapy based on the results of SNB and ALND that ranges from APBI to WBI with RNI. We initiated a prospective observational study on APBI with multicatheter brachytherapy after BCS. Data regarding the long-term efficacy of our technique indicated a few instances of local recurrence and a low rate of adverse events [26,27]. Therefore, APBI, rather than WBI, is primarily performed in node-negative patients. On the other hand, an additional RNI is administered to patients with ≥ 4 positive nodes.

In this study, we optimized our personalized radiation therapy ranging from APBI to WBI with RNI for breast-conserving treatment. First, the ability to select patients with ≥ 4 positive nodes as candidates for RNI using ALND was evaluated to assess the potential of personalized radiotherapy in SN-positive patients without ALND. Second, we compared different cohorts that received personalized radiation therapy on the basis of SNB and ALND.

2. Patients and Methods

2.1. Management of the Axilla and Personalized Radiotherapy after BCS

Before breast surgery, several imaging studies, including ultrasound (US), magnetic resonance imaging (MRI), and positron emission tomography/computed tomography (CT), were performed to evaluate axillary nodes for metastasis [28]. When axillary nodes were suspected as metastatic on the basis of any axillary imaging, US-guided fine needle aspiration (FNA) was performed to look for suspicious lymph nodes or axillary ultrasound was performed to identify the largest visible node. When axillary FNA revealed any evidence for metastases,

ALND was performed without SNB. Therefore, SNB was performed in the absence of evidence for positive axillary nodes. When SNs were revealed to be positive for metastasis by frozen section analysis, ALND was performed.

Multicatheter brachytherapy is considered to be an alternative to WBI in patients with negative SNs. Patients with ≥ 4 positive nodes were administered WBI with RNI administered to Level III/supraclavicular nodes. Other key APBI criteria were patient age of ≥ 40 years and maximum tumor diameter of ≤ 3.0 cm. This APBI registry study was approved by the institutional review board of our hospital. In WBI, patients received a total dose of 50 Gy in fractions of 2 Gy to the entire breast. Patients with risks, such as positive margins and young age, received a 10-Gy boost to the tumor bed. Combined RNI with WBI after BCS was performed in patients with ≥ 4 positive nodes (**Figure 1**).

2.2. APBI with Multicatheter Brachytherapy

The technique details of multicatheter brachytherapy as APBI have been previously reported [27,29]. The procedure involves insertion of applicators and delivery doses simulated by preoperative CT. Applicators for introduction of iridium wires were inserted according to preoperative CT-based simulation (**Figure 2**). The lumpectomy cavity was identified on postoperative CT scans with the help of hemoclips. The planned target volume was defined as the estimated tumor volume plus a 20-mm margin. Dose distribution analysis using dose-volume histograms was performed on the basis of postoperative CT. APBI was initiated on the day of primary surgery at a dose of 32 Gy in 8 fractions over 5 - 6 days. Fractions delivered twice daily were separated by an interval of at least 6 h.

2.3. Assessment of Outcomes

The prospective follow-up policy was designed so that

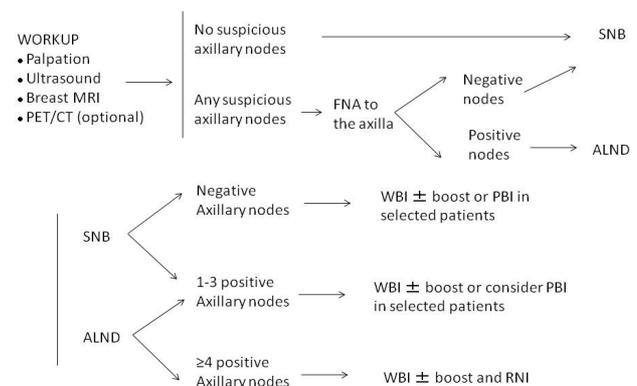


Figure 1. Management of axilla and personalized radiotherapy after breast-conserving surgery.

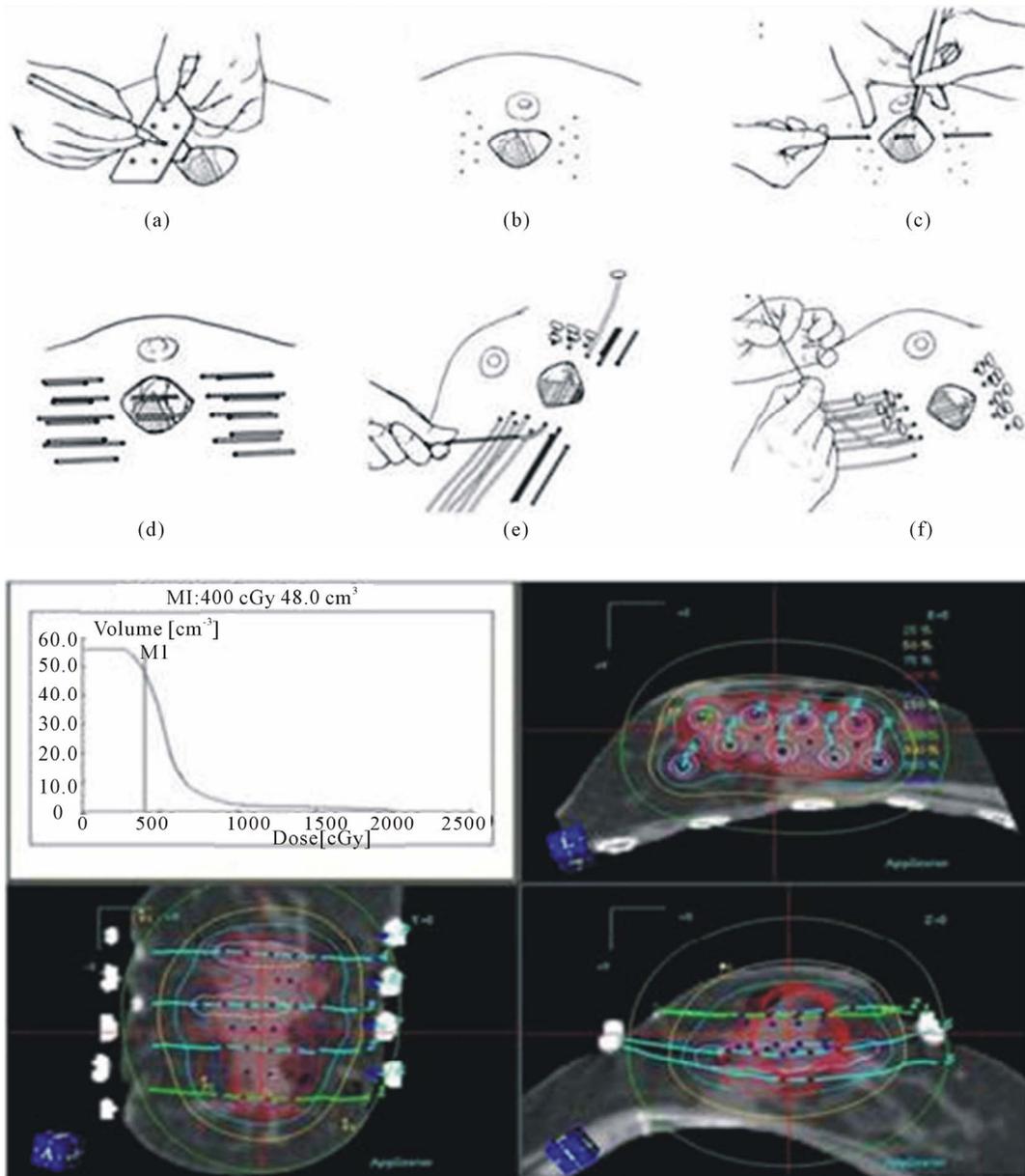


Figure 2. Implantation of multicatheters and optimization of treatment regimens.

all patients had a predefined schedule, including clinical examination every 3 - 4 months and annual mammography. Contrast-enhanced breast MRI was also performed every 12 months for the first 5 years of follow-up. For analysis, ipsilateral breast tumor recurrence (IBTR) was classified by clinical location in relation to the initial lumpectomy cavity. Tumor-bed recurrence (true recurrence) was defined as recurrence of the treated cancer within or immediately adjacent to the primary tumor site. Failure elsewhere was defined as IBTR several centimeters from the primary site and was generally considered to be a new primary cancer.

The chi-square test was used to analyze associations

among categorical variables with treatment groups. Student's unpaired t-test was used to analyze differences between 2 sample means of continuous variables. A p value of <0.05 was considered to indicate statistical significance. Statview 5.0 (SAS Institute Inc. Cary, NC, USA) was used to perform statistical analyses.

3. Results

3.1. Personalized Radiotherapy in SN-Positive Patients without ALND

Between August 2008 and April 2013, SNB using blue dye and radioisotopes was performed in 371 patients, and

ALND was performed without SNB in 55 patients with positive axillary FNA findings. Among the 371 patients who underwent SNB, ALND was performed in 52 because of positive SNs. For the patients with ≥ 4 positive nodes, RNI was combined with WBI for 12 (23.1%) patients who underwent SNB followed by ALND and for 32 (58.2%) patients who underwent ALND and were axillary FNA positive, respectively (**Table 1**). Therefore, among the ALND patients, those with positive axillary FNA findings had a significantly higher rate of requirement for RNI with WBI than those who underwent SNB ($p < 0.001$).

3.2. SN-Driven Personalized Radiation Therapy after BCS

A total of 317 consecutive patients who underwent BCS followed by radiotherapy since November 2007 were analyzed. Patients who received neoadjuvant chemotherapy were not enrolled in this study. A prospective multicatheter brachytherapy study on these patients was initiated in October 2008. A consort diagram is shown in **Figure 3**. **Table 2** lists the clinical, pathological, and treatment-related characteristics of the 2 groups. The mean age of the interstitial APBI patients (56.0 years) was significantly higher than that of the WBI patients; however, the difference was not significant (51.3 years, $p < 0.05$). APBI patients were more likely to have negative margins than WBI patients (86.1% vs. 77.9%, respectively; n.s.) and less likely to be node negative (86.6% vs.

Table 1. Potential of personalized radiotherapy in sentinel node-positive patients without axillary lymph node dissection (August 2008-April 2013).

	371 SNB followed by ALND	ALND with axillary FNA-positive status
Patients (n)	52	55
Positive nodes (mean)	2.4 (1 - 15)	8.7 (1 - 31)
Patients with ≥ 4 positive nodes (n)	12	32
Patients who required RNI (%)	23.1%	58.2%

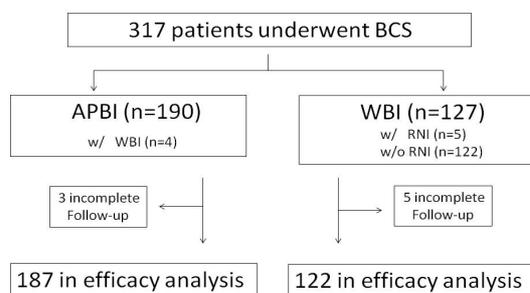


Figure 3. Consort diagram of radiotherapy after breast-conserving surgery.

Table 2. Patient demographics and tumor characteristics.

	APBI (2008.10-2013.4)	WBI (+RNI) (2007.11-2013.4)	p-value
Age (mean)	56.0 (30 - 92 y/o)	51.3 (31 - 84 y/o)	$p < 0.05$
<50	68 (36.4%)	58 (47.5%)	
50 - 59	46 (24.6%)	38 (31.2%)	
≥ 60	73 (39%)	26 (21.3%)	
Follow-up time (mean)	30.1 months	36.5 months	$p < 0.05$
Pathological diameter of invasive tumor (mean)	12.1 mm (0 - 38 mm)	12.3 mm (0 - 27 mm)	n.s.
Tis	18 (9.6%)	19 (15.6%)	
T1	156 (83.4%)	93 (76.2%)	
T2	13 (7.0%)	10 (8.2%)	
Margin negative	161 (86.1%)	95 (77.9%)	n.s.
Grades II-III	31 (16.6%)	24 (19.7%)	n.s.
ER positive	167 (89.3%)	105 (86.0%)	n.s.
HER2 overexpressed	17 (9.1%)	17 (13.9%)	n.s.
Node negative	162 (86.6%)	93 (76.2%)	$p < 0.05$
Adjuvant chemotherapy	52 (27.8%)	42 (34.4%)	n.s.

76.2%, respectively; n.s.). Further, patients in the APBI cohort received adjuvant chemotherapy less frequently than those in the WBI cohort (27.8% vs. 34.4%, respectively; n.s.).

3.3. Recurrence and Survival Rates

The treatment outcomes for the 2 cohort groups are shown in **Table 3**. With our follow-up period, loco-regional and distant recurrence were similar between the 2 groups. The local-only recurrence rate (IBTR) was 1.1% in the APBI group and 3.3% in the WBI group. The regional-only recurrence rate was 1.1% in the APBI cohort and 0.8% in the WBI group. The characteristics of the patients who experienced disease recurrence are also described in **Table 3**. There were 4 patients with distant recurrence only in the WBI cohort, and 1 death from other causes among the 2 arms.

4. Discussion

Breast cancer is the most frequently occurring cancer in Japan [30]. After the introduction of a mammography program to screen for breast cancer, the ratio of patients who underwent BCS increased, and this procedure became the most common treatment for breast cancer after 2003 [31,32]. Breast-conserving therapy consisting of BCS with radiotherapy has become the standard of care for early-stage breast cancer because of equivalent local control and survival for both BCT and mastectomy.

Table 3. Locoregional control and distant recurrence.

	APBI (n = 187)	WBI (+RNI) (n = 122)
Locoregional Recurrence		
Local only (IBTR)	2 (1.1%)	4 (3.3%)
Tumor bed recurrence	1	3
Failure elsewhere	1	1
Regional only	2 (1.1%)	1 (0.8%)
Local + regional	4 (2.1%)	5 (4.1%)
Distant Recurrence		
First or concurrent	0	4 (3.3%)
After locoregional	0	0

Moreover, according to a recent report, BCT was associated with improvement in overall survival and disease-specific survival regardless of age or hormone receptor status [33]. Although EBCTCG data demonstrated that omission of radiotherapy was one of the most relevant factors associated with local recurrence and the relationship between effects on local control and breast cancer mortality showed that 1 death from breast cancer could be avoided for every 4 local recurrences prevented [3,4], 20% of patients who underwent BCS in Japan did not receive WBI [34] because they had complete pathologically negative margins, occasional severe adverse events because of WBI, and long-term daily visits to radiation institutes.

Therefore, we previously initiated a prospective observational study of APBI with multicatheter brachytherapy as an alternative to WBI after BCS. Data regarding the long-term efficacy of our technique in Japanese breast cancer patients indicated a few instances of local recurrence and a low rate of adverse events [25,26].

In this study, we optimized our personalized radiation therapy ranging from APBI to WBI with RNI for breast-conserving treatment. The results demonstrated that clinical efficacy of APBI for local control after BCS was comparable to that of WBI \pm RNI at approximately 2.5 years of follow-up. The limitations of this study were that it was not randomized, was based on only a small number of participants, and covered only a short follow-up period. However, to the best of our knowledge, this is one of the largest observational studies from Asia to demonstrate the feasibility of BCT using multicatheter brachytherapy and with acceptable clinical outcomes.

In terms of “personalized radiotherapy after BCS”, many other factors other than axillary node status need to be considered because the risk of recurrence has been reported to be associated with not only the number of positive nodes but also various other factors (e.g., tumor subtype was recently claimed to be a factor relevant to local recurrence). The recent publication of the results of

the American College of Surgeons Oncology Group trial Z0011 demonstrated equivalent survival and local control in patients with 1 - 2 positive SNs who were randomly assigned to SNB alone or SNB followed by ALND [23]. The EORTC AMAROS trial has also shown that both ALND and axillary radiotherapy without ALND provided excellent regional control for SN positive patients [24]. The number of positive nodes was still important for the personalization of radiotherapy through several different approaches, from APBI to WBI with RNI. However, the number of positive nodes present cannot be determined if ALND is omitted.

When multi-image analyses and axillary FNA for suspicious lymph nodes have been introduced to select candidates for SNB, about 80% of SN-positive patients did not require RNI. On the other hand, if axillary FNA revealed metastatic lymph nodes, approximately 60% needed RNI because they had ≥ 4 positive nodes. Therefore, to extend “personalized radiotherapy after BCS”, we may adopt the following strategy: APBI (or WBI in selected patients) for SN-negative patients, WBI and ALND (or APBI and ALND in selected patients) for SN-positive patients, and WBI and ALND with or without RNI for axillary FNA-positive patients. Additional research information from several institutions is required, and randomized clinical trials to confirm the validity of the above strategy are warranted.

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