

Preliminary Results from a Multi-center Prospective Study (JROSG 05-5) on Postoperative Radiotherapy for Patients with High-risk Ductal Carcinoma in situ with Involved Margins or Margin Widths 1 mm or less than

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Abstract

Purpose: This prospective study aimed to evaluate the effectiveness of postoperative radiotherapy (PORT) consisting of whole breast irradiation followed by boost irradiation in patients with high-risk ductal carcinoma in situ (DCIS) with margin widths less than 1 mm.

Materials and Methods: A multi-center phase II study (Japanese Radiation Oncology Study Group: JROSG 05-5) was conducted to evaluate the effectiveness of PORT. PORT consisted of whole breast irradiation (50 Gy/25 fractions) followed by boost irradiation (10 Gy/5 fractions) using electron beams for patients with high-risk DCIS. Eligibility criteria were as follows: 1) DCIS without an invasive carcinoma component, 2) age between 20 and 80 years, 3) involved margins or margin widths less than 1 mm, 4) refusal of re-resection, 5) performance status of 0–2, and 6) written informed consent. The primary endpoint was ipsilateral breast tumor recurrence (IBTR), and secondary endpoints were overall survival, relapse-free survival, recurrence patterns, and adverse events.

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Results: Thirty-seven patients from 12 institutions were enrolled from January 2007 to May 2009. Median follow-up time was 45 months (range, 27–64 months). The median pathological tumor size was 2.5 cm (range, 0.3–8.5 cm). Twenty-one patients had close margins, and 16 had involved margins. Four-year IBTR, overall survival, and relapse-free survival rates were 3% (95% confidence interval (CI): 0–20), 97% (95% CI: 82–100), and 94% (95% CI: 77–99), respectively.

Conclusions: Our preliminary results suggest that this PORT schedule may be promising for patients with high-risk DCIS. However, to make any definitive conclusions, a longer follow-up time is required.

Keywords: Ductal carcinoma in situ; Breast cancer; Margin width; Radiotherapy; Breast conservation

1. Introduction

Ductal carcinoma in situ (DCIS) is a slow growing tumor of the breast tissue that is less aggressive than other forms of cancer. Many such tumors require radiotherapy or surgical treatment (Schwartz, G., et al., 1999, Punglia, R.S., et al., 2013). Mammography screenings increase the opportunity for treatment of patients with DCIS (Ernster, V., et al. 1996). In the United States, by 2013, approximately 64,640 new DCIS diagnoses will be made, constituting approximately 22% of all new breast cancers (Silgel, R., et al., 2013). Breast conserving therapy, including partial resection followed by breast irradiation, has been one of the standard treatments for DCIS (Punglia, R.S., et al., 2013). Several randomized clinical trials have demonstrated that postoperative radiotherapy (PORT) decreases the risk of ipsilateral breast tumor recurrence (IBTR) (Fisher, B., et al., 1993; Fisher, B., et al., 1998; Houghton, J., et al., 2003; Julien, J., et al., 2000). However, these randomized trials have mainly included low-risk patients with negative surgical margins. There has been little evidence supporting treatment strategies for patients with high-risk DCIS and either a positive surgical margin or a narrow distance between surgical margins and tumor cells.

Silverstein et al. (1996) developed a prognostic model that included tumor size, margin width, and pathological classification (the Van Nuys Prognostic Index; VNPI). Patients with high VNPI scores (e.g., 8 or 9) showed high rates of IBTR, after receiving PORT. In contrast, the eight-year IBTR rate among patients with low VNPI scores (e.g., 3 or 4) was low regardless of whether or not PORT was used (100% vs. 97%). Silverstein et al. (1999) reported that patients with tumor margin widths less than 1 mm could benefit from PORT, with an eight-year IBTR rate of approximately 30%. However, this retrospective study included a variety of PORT schedules. Few prospective studies have evaluated the role of PORT exclusively for high-risk DCIS, and a maximally-effective treatment schedule has not yet been established. The present prospective study aimed to evaluate the effectiveness of PORT consisting of whole breast irradiation followed by boost irradiation in patients with high-risk DCIS and tumor margin widths less than 1 mm.

2. Materials and Methods

A multi-center phase II study (Japanese Radiation Oncology Study Group: JROSG 05-5) was conducted to evaluate the effectiveness of PORT consisting of tangential whole breast irradiation (50 Gy/25 fractions) followed by boost irradiation (10 Gy/5 fractions) of the tumor bed using electron beams for patients with high-risk DCIS. Patients were eligible for inclusion in the study if

they: 1) had DCIS without an invasive carcinoma component, 2) were between 20 and 80 years of age, 3) were diagnosed as having involved margins or margin widths less than 1 mm after pathological evaluation using 5 mm thick specimens, 4) refused re-resection, 5) had a performance status of 0–2, and 6) provided written informed consent. Exclusion criteria were: 1) bilateral breast cancers, 2) diffuse calcification, 3) multiple tumors, 4) macroscopic residual tumor, 5) positive axillary lymph node metastases, 6) past history of chest irradiation, 7) collagen vascular disease, 8) pregnancy, 9) active double cancer, 10) mental disorders, 11) uncontrolled diabetes, 12) uncontrolled hypertension, and 13) cardiac disease.

Radiation Treatment Planning

All patients were placed in the supine position, and underwent computed tomography (CT) as part of the radiation treatment planning. CT scanning was performed, with slices extended to completely cover the bilateral whole breast, lungs, heart, and lower neck. No respiratory control was used. All patient procedures were planned using three-dimensional conformal radiotherapy (3D-CRT) treatment planning software. To correctly evaluate heterogeneous tissue density, the analytical anisotropic algorithm, a superposition algorithm, convolution algorithm, or AAA algorithm was used. Whole breast irradiation was comprised of tangential beams using 4 or 6 MV photons. Simulation planning was used to minimize radiation to at-risk organs, and to modify homogeneous doses to fit target volumes using a wedge filter. Beam weights, beam angles, and wedge angles were manually optimized. A total dose of 50 Gy in 25 fractions for whole breast irradiation was defined at the reference point (isocenter). The isocenter was placed in the center of the radiation field or vicinity. The electron beam width for boost irradiation of the tumor bed was determined according to surgical clips, surgical cavity, and pathological findings (e.g., 3 cm-margin). Appropriate electron beam energy was selected according to the depth of the tumor bed.

Endpoints and Statistical Analyses

The primary endpoint was the IBTR, and secondary endpoints were overall survival (OS), relapse-free survival (RFS), recurrence patterns, and adverse events. IBTR was defined as recurrence (invasive carcinoma or DCIS) in the ipsilateral irradiated breast. OS time was defined as the time from registration to death (due to any cause). RFS time was defined as the time from registration to treatment failure (in the ipsilateral breast, axillary node, or at a distant site) or death (due to any cause). Toxicities were evaluated according to Common Terminology Criteria for Adverse Events (CTCAE) version 3.0. The five-year estimated IBTR rate was projected as 20% and the low five-year IBTR rate threshold was set at 45%. It was estimated that a sample of 36 patients was required, with a one-sided alpha of 0.05 and a statistical power of 90% (assuming several patients would be lost to follow-up). Kaplan-Meier methods were used to estimate IBTR, OS, and RFS. All enrolled patients were included in the primary endpoint assessment (an intention-to-treat analysis).

3. Results

This protocol concept was accepted in October 2005, and the full protocol was accepted in August 2006 by the executive Japanese Radiation Oncology Study Group (JROSG) committee. Thirty-seven patients from 12 institutions were enrolled from January 2007 to May 2009. The median patient follow-up time was 45 months (range, 27–64 months), median patient age was 52 years (range,

33–78 years), and median pathological tumor size was 2.5 cm (range, 0.3–8.5 cm). Patient characteristics are shown in Table 1.

Table 1 Patient Characteristics

	n (%)	
Age (years)		Median 52 (33–78)
30–39	3(8)	
40–49	11(30)	
50–59	14(38)	
60–70	6(16)	
≥70	3(8)	
Pathological diameter (cm)		Median 2.5 (0.3–8.5)
≤1.9	15(41)	
2–3.9	6(16)	
4–5.9	7(19)	
≥6	9(24)	
Estrogen receptor		
Positive	26(70)	
Negative	7(19)	
Unknown	4(11)	
Progesterone receptor		
Positive	22(60)	
Negative	11(30)	
Unknown	4(10)	
Margin status		
Close margin	16(43)	
Involved margin	21(57)	

Sixteen patients had close margins, and 21 had involved margins. All patients received PORT per-protocol, and no patient interrupted PORT. Fourteen (38%) patients received adjuvant hormonal therapy.

The four-year IBTR, OS, and RFS rates were 3% (95% confidence interval [CI]: 0–20), 97% (95% CI: 82–100), and 94% (95% CI: 77–99), respectively (Figure 1).

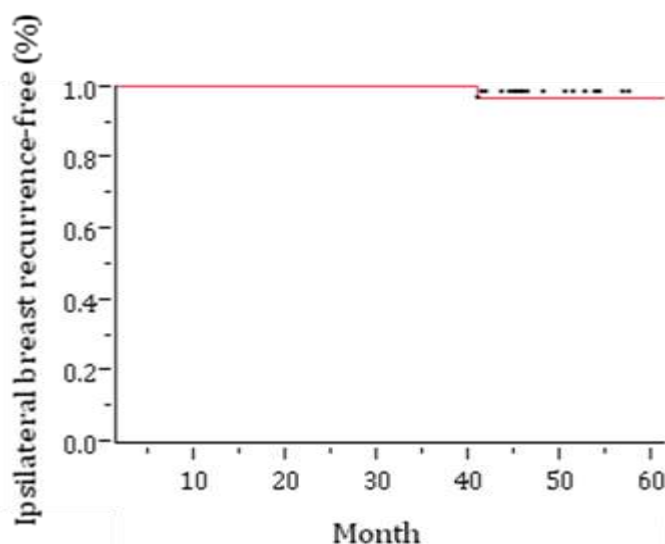


Fig 1. Ipsilateral Breast Tumor Recurrence-Free Survival Curve

One patient with close margins, who received adjuvant tomosifen, developed local recurrence at the original site after 39 months. She underwent a salvage mastectomy, and the pathological diagnosis was DCIS without an invasive carcinoma component. One patient died of colon cancer 28 months after registration, without experiencing breast cancer recurrence. No recurrence events were identified in regional lymph nodes or distant sites, and no severe adverse events (Grade 3 or 4) have been reported to date.

4. Discussion

The current standard of care for patients with DCIS includes mastectomy and breast conserving therapy. The Canadian population-based registries demonstrated that the frequency of mastectomy for patients with DCIS decreases yearly, and that only 19% of DCIS patients underwent mastectomy between 1990 to 2000 (Rakovitch, E., et al., 2003). Mastectomy is still considered a standard treatment for patients with diffuse infiltrative disease, large tumors, or positive surgical margins after repeated resection. The incidence of axillary lymph node metastases is very low, and the roles of axillary lymph node dissection and sentinel lymph node biopsy have not yet been established (Cox, C., et al., 2001). If the existence of invasive carcinoma is suspected, however, axillary management, including axillary lymph node dissection and sentinel lymph node biopsy, is considered.

There remains room for discussion regarding whether all patients with DCIS should be treated. Although it is uncertain what the probability of progression is, it has been suggested that the lifetime risk of DCIS progression is considerably less than 50% (Welch, H.G. et al., 2008). Studies have also indicated that PORT after partial resection reduces the IBTR rate by approximately 60% (Kuerer, H.M., et al., 2009). One half of patients who experience local recurrence after breast conserving therapy have invasive carcinoma, and other has non-invasive carcinoma. There have been no reports showing that the omission of PORT increases distant metastases or decrease OS.

The main goal of DCIS management is to reduce the risk of progression to invasive carcinoma (Punglia, R.S., et al., 2013), and the secondary goal is to avoid patients having to undergo salvage mastectomy. However, in the United States, population-based analyses have revealed that, among patients who receive partial resection for DCIS, approximately half do not receive PORT, with substantial variation in the use of this treatment (Punglia, R.S., et al., 2013).

Silverstein et al. (1996) developed the VNPI model for patients with DCIS, which includes tumor size, surgical margin width, and pathological findings. Dunne et al. (2009) conducted a systematic review and reported that a margin threshold of 2 mm seemed to be as good as a larger margin when breast conserving surgery for DCIS is combined with PORT. Wang et al. (2012) conducted a meta-analysis of margin threshold for patients with DCIS. This study reported that, as compared with a negative tumor margin greater than 2 mm, a negative tumor margin of at least 10 mm was associated with a lower risk of IBTR (odds ratio(OR)=0.46, 95% CI: 0.29–0.69). Silverstein et al. (1999) reported that patients with tumor margin widths less than 1 mm could benefit from PORT, with an eight-year IBTR probability of 30% and approximately 80% of recurrence developing within three years. This retrospective study included various radiotherapy schedules (e.g., dose of whole breast, 40 to 50 Gy), with boost irradiation (16 to 20 Gy) being delivered to the tumor bed via brachytherapy or electron beam therapy. Only a few prospective studies have evaluated the role of PORT exclusively in high-risk patients with DCIS. The preliminary results of this prospective study showed that the four-year IBTR rate was only 3% after PORT. This preliminary result indicated that PORT, consisting of tangential whole breast irradiation (50 Gy/25 fractions) followed by boost irradiation (10 Gy/5 fractions) of the tumor bed was a promising schedule for high-risk patients with DCIS.

The limitations of this study are its small sample size and short follow-up time. In addition, a central pathological review has not been conducted. Although a central pathological review system was not established prior to this prospective trial, it was determined that the method of pathological evaluation of resection samples would be conducted using a 5 mm thick slice. This technique is believed to provide accurate pathological evaluation of tumor extension and margin width.

5. Conclusions

Our preliminary results suggest that this radiotherapy schedule could be promising for patients with high-risk DCIS. A longer follow-up time is required, however, to make any definitive conclusions.

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Conflicts of Interest

The authors have no conflicts of interest to declare.

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