Symptomatic Radiation Pneumonitis After Accelerated Partial Breast Irradiation Using Three-dimensional Conformal Radiotherapy

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Abstract. *Aim: To examine the relationship between symptomatic radiation pneumonitis and lung dose-volume parameters for patients receiving accelerated partial breast irradiation (APBI) using three dimensional-conformal radiotherapy (3D-CRT). Patients and Methods: The prescribed radiation dose was 30 Gy in 5 fractions over 10 days. Toxicity was graded according to the Common Terminology Criteria for Adverse Events (version 4.0). Results: Fifty-five patients were enrolled from August 2010 to October 2013 and the median follow-up time was 30 months (range=18-46 months). Three patients (5%) developed grade 2 symptomatic radiation pneumonitis after 3D-CRT APBI. Among 16 patients with ILV_{10Gy} (% ipsilateral lung receiving ≥10 Gy) of 10% or higher, three patients (19%) developed symptomatic radiation pneumonitis. This trend was not observed in any of the patients with ILV_{10Gy} less than 10% (p=0.005). Conclusion: High ILV_{10Gy} might be associated with symptomatic radiation pneumonitis after 3D-CRT APBI.*

Breast-conserving therapy, consisting of partial resection followed by postoperative whole-breast irradiation and/or boost irradiation, has been the standard-of-care for patients with early breast cancer (2). Approximately, 90% of ipsilateral breast recurrences after breast-conserving therapy develop in the vicinity of the tumor bed (10, 13, 15). Given this recurrence pattern, the concept of accelerated partial breast irradiation (APBI) using small radiation fields and a large fraction size has been designed to reduce the radiation treatment period without increasing the risk of breast recurrences and toxicities (10, 13). The large irradiated volume of normal tissues is associated with the risk of toxicities and cosmetic compromise (4, 5, 15). Symptomatic radiation pneumonitis leads to depress the patient's quality of life. The confidential dosimetric parameters for the risk of symptomatic radiation pneumonitis after 3D-conformal radiotherapy (3D-CRT) APBI have not been established because of its infrequent incidence, small sample size and various treatment schedules (12). We aimed to examine the relationship between the risk of symptomatic radiation pneumonitis and dose-volume parameters for patients enrolled in our prospective study for 3D-CRT APBI using 30 Gy in 5 fractions over 10 days.

Patients and Methods

Eligibility criteria for enrollment in the prospective study. Eligibility criteria for this prospective study were as follows: (i) elderly patients aged between 50 and 80 years, (ii) Eastern Cooperative Oncology Group performance status of 0 or 1, (iii) pathological diameter of invasive component ≤2 cm, (iv) invasive carcinoma, (v) single tumor, (vi) positive estrogen receptor, (vii) distance between the surgical edge and cancer cell ≥2 mm, (viii) cranio-caudal surgical clip distance (CCD) ≤5.5 cm, (ix) no axillary lymph node metastasis and (x) written informed consent. Exclusion criteria included: active second malignancy, uncontrolled infection, pregnancy, mental disorder, uncontrolled diabetes mellitus, interstitial pneumonitis,

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collagen vascular diseases, heart failure and previous history of radiofrequency ablation. The primary end-point of this trial was the rate of 2-year adverse events of grade 2 or worse. This study was approved by the Institutional Review Board and initiated in August 2010 (Registration number: UMIN000004184).

Surgical and radiation treatments. All enrolled patients underwent partial breast resection and four or five surgical clips were placed at the borders of the surgical bed. The sentinel node biopsies and axillary node dissection were allowed. All patients were placed in the supine position for radiation treatment planning computed tomography (CT). The clinical target volume (CTV) was defined as the volume bound by uniform expansion of surgical clips by 1.5 cm in all dimensions, excluding the pectoral muscles, chest wall, lung, heart, pericardial fat and 5 mm beneath the skin. The planning target volume (PTV) was defined as the volume bound by uniform expansion of CTV by 1.0 cm in all dimensions. The planning target volume for evaluation (PTV_EVAL) was specified as defined by the volume of PTV excluding the first 5 mm of tissue under the skin, the posterior breast tissue extent (chest wall and pectoral muscles), lung and heart. The ipsilateral breast volume (IBV) was defined as the volume of ipsilateral breast tissue encompassing typical whole breast tangent but excluding pectoral muscles. Planning was conducted using 3D-CRT planning system software Xio version 4.6.2 (Elekta, Stockholm, Sweden), Eclipse version 8.0 (Varian Medical Systems Inc., Palo Alto, CA, USA), Pinnacle^3 version 8.0m (Pinnacle Treatment System; Philips, Milpitas, CA, USA) and iPlan RT version 4.5.1 (BrainLab Co., Heimstetten, Germany). Radiotherapy planning and dose-volume histogram (DVH) constraints for normal tissues were applied according to our previous report (14). Beam arrangements included mainly non-coplanar 4- or 5-field beams using 6 MV photons and multi-leaf collimator with 5-mm leaf width. Beam weight, beam angle and wedge angles were manually optimized, such that the targeted goal was to cover the PTV_EVAL by a dose ≥95% of the prescribed dose. A total dose of 30 Gy in 5 fractions was prescribed to the reference point dose (iso-center) according to the International Commission on Radiation Units and Measurements (ICRU) 50 (1).

Patients' follow-up and data analysis. Patients were examined at 2, 4 and 6 months after the trial registration and monitored every 6 months for 2 years. The toxicity was graded according to the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE version 4.0). Symptomatic radiation pneumonitis was graded according to the worst grade score amongst these grades including "Dyspnea", "Cough" and "Respiratory, thoracic and mediastinal disorders - Other, specify" until the last follow-up date. DVHs were calculated to determine the ipsilateral lung volume (ILV) receiving 20 Gy or higher (ILV_{20Gy}), 13 Gy or higher (ILV_{13Gy}), 10 Gy or higher (ILV_{10Gy}) and 5 Gy or higher (ILV_{5Gy}) (12). Statistically significant differences between two samples' means and medians for continuous variables were analyzed using the Student's unpaired *t*-test. $p<0.05$ was considered statistically significant. Statistical analysis was performed using JMP software version 11 (SAS Institute, Cary, NC, USA).

Results

Patient's characteristics and dose constraints. From August 2010 to October 2013, 55 patients were enrolled. The median age was 63 years (range=50-79). Patients' characteristics are shown in Table I. All patients received a sentinel node biopsy and no one received axillary dissection. Fifty-three patients were treated with photon beams alone, while two patients were treated using combined beams' techniques with photons and electron beams. Hormonal therapy was administered to 52 patients (95%), whereas no patient received systemic cytotoxic agents.

Table I. *Patients' characteristics*.

	Number	Median (range)
Age (years)		63 (50-79)
Side of breast		
Right	29	
Left	26	
Site of tumor		
Medial	16	
Lateral	39	
Breast volume (cm^3)		
Right		859 (451-1804)
Left		821 (373-1842)
Pathological diameter (cm)		1.2 (0.1-2.0)
Axillary management		
Sentinel node biopsy	55	
Axillary dissection	0	
Hormone therapy		
Received	52	
Not received	3	
Chemotherapy		
Received	0	
Not received	55	

Pulmonary adverse events. Median follow-up time was 30 months (range=18-46). No patient developed ipsilateral breast recurrence, regional node recurrence or distant metastasis until the last follow-up date. There were three patients (5%) who developed grade 2 symptomatic radiation pneumonitis at 5, 8 and 9 months after 3D-CRT APBI. No patient experienced any grade 3 or 4 adverse events. The three patients with symptomatic radiation pneumonitis had ipsilateral pulmonary infiltrates with organizing pneumonitis (Figure 1). All three patients had right breast cancer; two patients received hormonal therapy and one patient did not. They complained of fever, cough and short of breath, thus, they received oral prednisone for various durations. These symptoms ameliorated after several weeks of prednisone administration. No patient developed chronic pulmonary fibrosis. Three patients who developed symptomatic radiation pneumonitis had ILV_{10Gy} of 10.9%, 12.0% and 13.6%, respectively (Figure 2). Among 16 patients with ILV10Gy of 10% or higher, three patients (19%) developed symptomatic radiation pneumonitis. Such a trend was not recorded in patients with ILV_{10Gy} less than 10% ($p=0.005$).

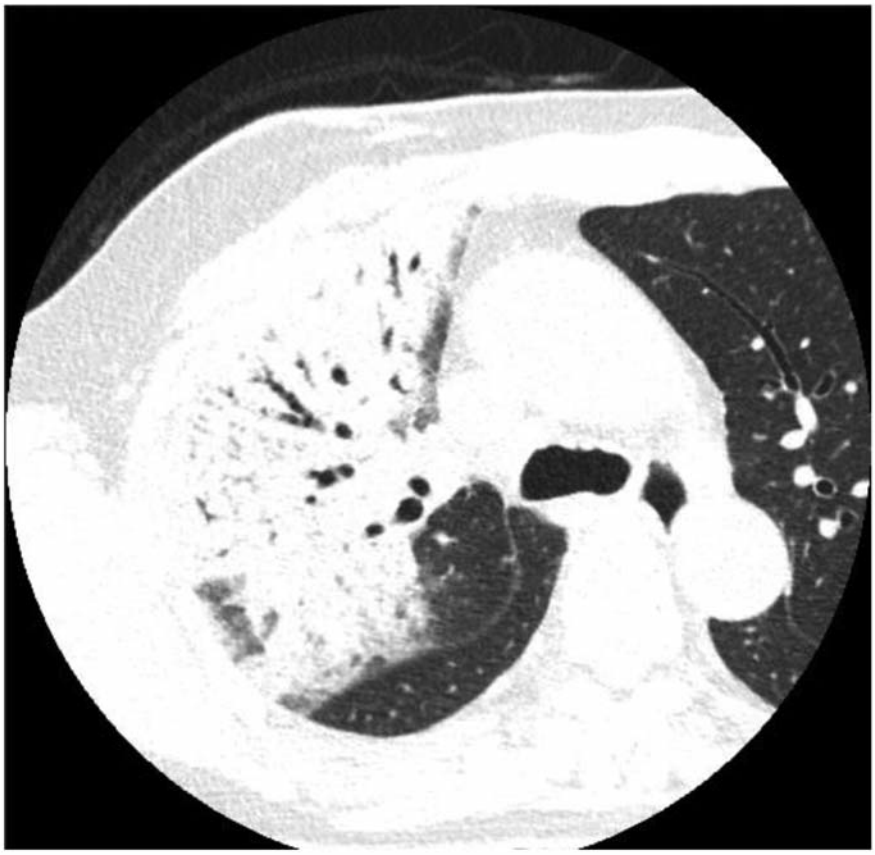

Figure 1. *A 61-year-old woman with cancer in her right breast developed symptomatic radiation pneumonitis five months after accelerated partial breast irradiation. The chest computed tomography image demonstrated pulmonary infiltration and air bronchogram.*

Three patients, among 12 patients with ILV_{13Gy} of 8% or higher, developed symptomatic radiation pneumonitis; however, patients with ILV_{13Gy} of less than 8% did not (p=0.003). ILV_{20Gy} (≥3% *vs.* <3%) and ILV_{5Gy} (≥20% *vs.* <20%) were not associated with the risk of symptomatic radiation pneumonitis (p=0.17 and p=0.11, respectively).

Discussion

Symptomatic radiation pneumonitis should be distinguished from non-symptomatic radiographic changes without pulmonary dysfunction. Symptomatic radiation pneumonitis usually occurs within 10 months after completion of radiotherapy and seldom occurs beyond one year (9). Kahan and colleagues reported that the radiation dose to 25% of the ipsilateral lung volume ($D_{25\%}$) and ILV_{20Gy} were associated with any grade radiation-induced lung damages after conventional tangential breast irradiation (7). On the other hand, Ogo and colleagues reported that there was no relationship between radiation parameters and organizing pneumonitis (11).

Recht and colleagues evaluated 198 patients who were enrolled in their prospective dose-escalation study of 3D-CRT APBI (12). Patients received 32 or 36 Gy in 4 Gy fractions, given twice daily over one week. Among twenty nine patients who were treated with 36 Gy using pure photon beams, four patients (14%) developed symptomatic radiation pneumonitis. They evaluated the relationship between symptomatic radiation pneumonitis (≥grade 2) and dosimetric parameters recommending that ILV_{20Gy} should be lower than 3%, ILV_{10Gy} lower than 10% and ILV_{5Gy} lower than 20% to reduce the risk of symptomatic radiation pneumonitis. Graham and colleagues evaluated the relationship between DVH parameters after 3D-CRT for non-small cell lung cancers and symptomatic radiation pneumonitis after radiotherapy with or without chemotherapy and reported that an irradiated lung volume of 20 Gy or higher (V_{20}) was a useful parameter to estimate the risk of symptomatic radiation pneumonitis (3). Jain and colleagues compared the dosimetric parameters of the pulmonary toxicities after the different treatment schedules for breast cancer using biologically equivalent dose (BED) calculations

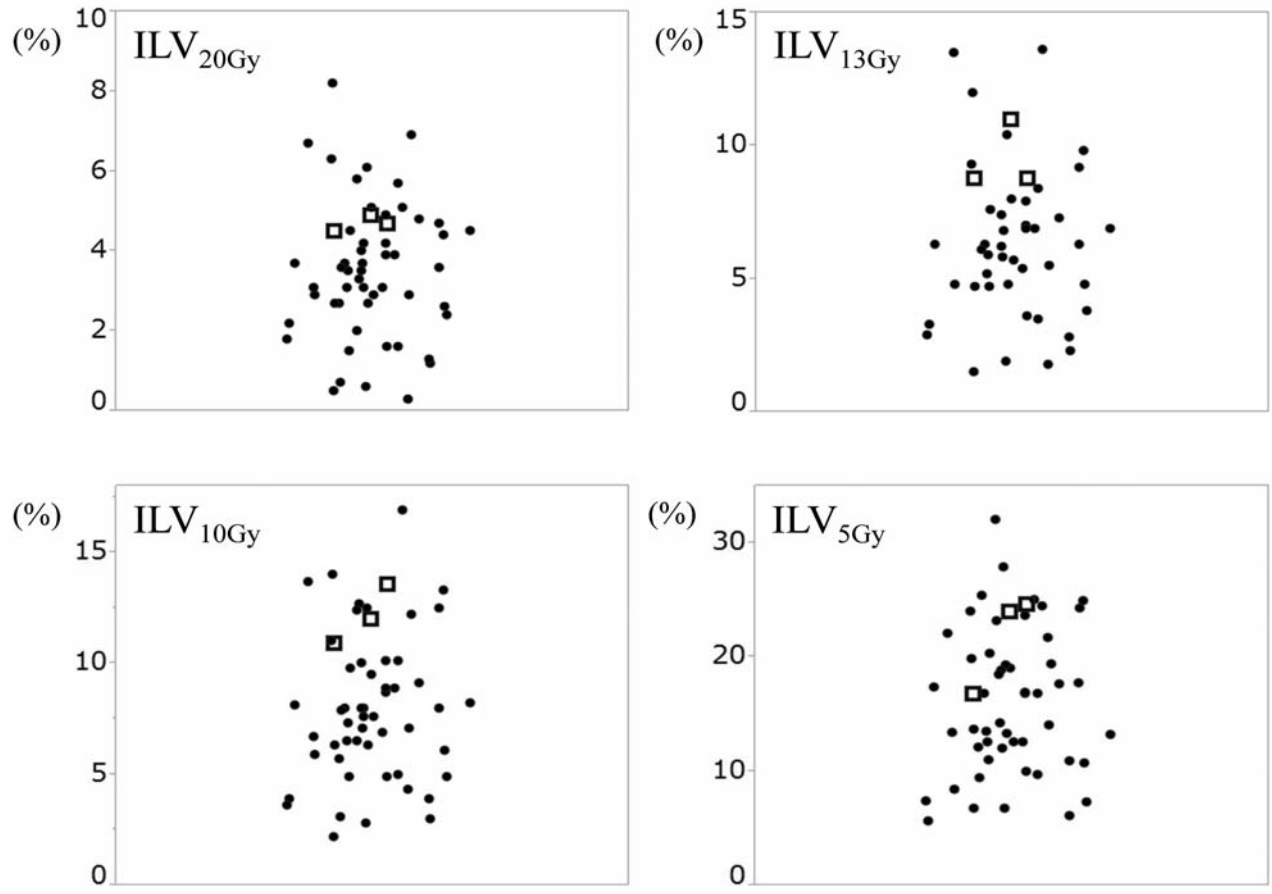

Figure 2. *The ipsilateral lung volume (ILV) receiving 20 Gy or higher (ILV_{20Gy}), 13 Gy or higher (ILV_{13Gy}), 10 Gy or higher (ILV_{10Gy}) and 5 Gy or higher (ILV_{5Gy}) of all patients was plotted. Open squares show patients who developed symptomatic radiation pneumonitis and black circles show patients who did not.*

(6). When "n" is defined as the number of fractions and "d" is defined as the dose per fraction, BED could be calculated using the following formula:

BED=nd[1+d/(alpha/beta)]

They estimated the alpha-beta ratio of late adverse effects, including pneumonitis at 3 Gy, and they calculated the BED (Gy_3) of the ipsilateral lung that received 20 Gy delivered in 25 fractions for patients who were treated with the conventional fractionated tangential-field whole breast irradiation using 50 Gy in 25 fractions:

BED (Gy_3)=25×0.8×(1+0.8/3)=25.3 (Gy_3)

When we apply the 3D-CRT APBI schedule of 30 Gy in 5 fractions, the same BED (Gy_3) value of the ipsilateral lung could be obtained using the following formula:

25.3 Gy_3=5×d×(1 + d/3)

The solution of "d" is approximately 2.68 and the irradiated lung volume receiving 13.4 Gy (2.68 Gy × 5 fractions=13.4 Gy) or higher could be supposed to have the same clinical value of V_{20} for patients with lung cancers. Our study showed that high ILV_{13Gy} and high ILV_{10Gy} were associated with symptomatic radiation pneumonitis.

Livi and colleagues conducted a phase III trial comparing APBI using intensity modulated radiotherapy (IMRT) of 30 Gy in 5 fractions given each other day with the conventional fractionated tangential-field whole breast irradiation (8). They demonstrated that no patient developed symptomatic radiation pneumonitis after IMRT APBI. The DVH profiles of IMRT APBI seem to be different from those of 3D-CRT APBI and, thus, a definitive conclusion on confidential dose constraints for symptomatic pneumonitis after various APBI schedules could not be reached (15).

There are several limitations to our study. First, there were few pulmonary adverse events after 3D-CRT APBI not allowing to achieve definitive conclusions on dosimetric

parameters for risk of symptomatic radiation pneumonitis. Second, our treatment schedule is different from the common APBI schedule of 38.5 Gy in 10 fractions over 5 days, that was applied in a number of studies. Therefore, our dosimetric parameters for the risk of symptomatic radiation pneumonitis should be validated by further studies.

Conflicts of Interest

None.

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