Case report of a dose-volume histogram analysis of rib fracture after accelerated partial breast irradiation: interim analysis of a Japanese prospective multi-institutional feasibility study

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Abstract

We initiated the first multi-institutional prospective study of accelerated partial breast irradiation for early breast cancer in Japan. Our early clinical results showed that the treatment methods were technically reproducible between institutions and showed excellent disease control at a median follow-up of 26 months in our previous report. At present, total 46 patients from six institutions underwent the treatment regimen from October 2009 to December 2011, and the median follow-up time was 60 months (range, 57-67 months). In 46 patients, we experienced one patient who had rib fracture as a late complication. The dose-volume histogram (DVH) result of this patient was analyzed. The D0.01cc, D0.1cc, and D1cc values of the patient were 913, 817, and 664 cGy per fraction, respectively. These values were the highest values in 46 patients. The average D0.01cc, D0.1cc, and D1cc values of the other 45 patients were 546, 500, and 419, respectively, cGy per fraction. From this result, DVH values showing high-dose irradiated volume (D0.01cc, D0.1cc, and D1cc) seem to be a good predictive factor of rib fracture for accelerated partial breast irradiation. However, further investigation is necessary because of the small number of patients investigated.

Key words: breast cancer, accelerated partial breast irradiation, dose-volume histogram, rib fracture.

Purpose

Breast-conserving surgery with postoperative radiation therapy is a standard of care for early breast cancer. The most common radiation therapy technique is whole-breast radiotherapy (WBRT), which has been proven to reduce the rate of local recurrence by one-third [1,2]. However, completion of WBRT takes 5 to 6 weeks, which is sometimes a problem for working patients or with...
Dose-volume histogram analysis of rib fracture after accelerated partial breast irradiation

Accelerated partial breast irradiation (APBI) may present a solution to the issues associated with WBRT. This method requires a much shorter treatment time (e.g., one day [5] to several days) than WBRT. Recently, the results of a phase III clinical trial in Europe were published and demonstrated the non-inferiority of APBI when compared with whole-breast irradiation [6]. In Japan, APBI was introduced in 1998 and showed good preliminary results [7,8]. The present study is the first multi-institutional prospective study of APBI in Japan. Early clinical results, including detailed treatment methods, have been published [9,10,11]. The results showed that the treatment methods were technically reproducible between institutions and showed excellent disease control at a median follow-up of 26 months [10]. However, we reported one patient who experienced rib fracture as a late complication [10]. This is a rare complication in patients who receive WBRT. In this report, we analyze the dose-volume histogram (DVH) of the rib to evaluate the threshold doses for rib fracture.

Case report

The treatment protocol was registered at the University Hospital Medical Information Network Clinical Trials Registry and was approved by participating institutional review boards. Patient eligibility criteria are summarized in Table 1. Although molecular subtype should be included or not is controversial [12], we did not include Her2 status. Forty-six patients from six institutions underwent treatment regimen from October 2009 to December 2011. The median follow-up time was 60 months (range, 57-67 months). Written informed consent was obtained from all patients.

All patients underwent breast-conserving surgery, in which surgical clips were implanted in the resection margins. We confirmed the presence of negative surgical margins and negative metastatic lymph nodes before radiation. Applicators were generally implanted in two or more planes.

Treatment plans were calculated by three-dimensional brachytherapy planning. In planning computed tomography (CT) images, 15 mm radius balloons were drawn around the surgical clips. The spaces between the balloons were interpolated clinically, and the reproduced volume was defined as the clinical target volume (CTV). To reduce the interobserver variations of CTV delineation [13], a dummy run was completed, and one physician (KY) participates in the treatment for a first patient of almost all institutes. The skin (5 mm thickness from the surface) and chest wall were excluded from the target volume. In numerous planning methods [14], we used the Paris dose calculation system with manual modifications. The prescribed doses were 36 Gy per six fractions in 3 days, with an interval of 6 hours between two fractions on the same day. This dose-fractionation schedule is biologically similar to schedules of Hungary group [15] and Azerbaijan group [16]. High-dose-rate brachytherapy with an Ir-192 source was used.

To control the quality of brachytherapy, dose constraints were set as follows. The reference volume (Vref), which was the irradiated volume receiving ≥100% of the prescribed dose was principally limited to less than 150 cm³. The dose non-uniformity ratio (DNR), which was defined as \( V_{1.5\text{ref}}/V_{\text{ref}} \) was less than 0.35. \( V_{1.5\text{ref}} \) is the irradiated volume receiving ≥150% of the prescribed dose. The clip dose had to be more than or equal to 6 Gy per fraction.

The rib was drawn into the planning CT as an organ at risk, and the minimum dose received by the maximally irradiated 0.01, 0.1, and 1 cc volumes (\( D_{0.01\text{cc}} \), \( D_{0.1\text{cc}} \), and \( D_{\text{1cc}} \)) were calculated. Systemic therapy was performed according to each institute’s treatment policy. Chemotherapy was not allowed during the protocol treatment period and for 2 weeks thereafter. All clinical data were prospectively collected every 2 weeks for 1 month, every 3 months until 24 months after treatment, and every 6 months thereafter up to 60 months. These items were scored by the physician according to the Common Terminology Criteria for Adverse Events ver. 3.0 (CTCAE v3).

The case patient was a 43-year-old woman with an adenocarcinoma on the left breast that was staged pT2N0M0 using the 2002 UICC classification. The tumor was positive for estrogen and progesterone receptors. Fifteen flexible applicator tubes were implanted (Figure 1A). She complained of chest wall pain 9 months after treatment, and the CT image showed rib fracture at 11 months after treatment (Figure 1B). The fracture was judged as Grade 2 of CTCAE v3, and it healed 18 months after treatment.

The DVH result of this patient is that \( V_{\text{ref}} \) and \( V_{1.5\text{ref}} \) were 112 cc and 34.7 cc, respectively, and the DNR was 0.31. CTV volume was 40 cc. Eight clips were implanted, and the clip doses were 713 to 1,083 cGy per fraction. \( D_{0.01\text{cc}} \) (CTV) and \( D_{100} \) (CTV) were 696 and 614 cGy per fraction, respectively. The \( D_{0.01\text{cc}} \), \( D_{100} \), and \( D_{\text{1cc}} \) values of the

| Table 1. Patient eligibility criteria |
|-----------------------------|
| Female invasive/noninvasive ductal/lobular cancer ≤ 3 cm |
| Age ≥ 35 years               |
| Written informed consent    |
| Performance status: 0 or 1  |
| No collagen vascular diseases except rheumatoid arthritis |

No performance status except rheumatoid arthritis
rib were 913, 817, and 664 cGy per fraction, respectively. The $D_{0.01cc}$, $D_{0.1cc}$, and $D_{1cc}$ values for the total six fractions were 54.8, 49.0, and 39.8 Gy, respectively. The biologically equivalent doses that were calculated as equivalent 2 Gy fractions (EQD$_2$) were 132.9, 109.5, and 76.8 Gy ($\alpha/\beta = 3$). The average $D_{0.01cc}$, $D_{0.1cc}$, and $D_{1cc}$ values of the other 45 patients were 546, 500, and 419 cGy per fraction, respectively.

We present these DVH values of the rib for all 46 patients (Figure 2A-C). DVH values of this patient were higher than those of other 45 patients.

Discussion

Rib fracture after conventional radiotherapy generally has a low incidence. However, hypofraction radiotherapy schedule seems to be associated with a higher rate of rib fracture. Nambu et al. reported the results of stereotactic body radiotherapy (SBRT) for lung cancer [17]. They administered 48 to 70 Gy per 4 to 10 fractions. Rib fracture was observed in 14/41 (34%). Proton therapy was also associated with a higher rate of rib fracture. Kanemoto et al. reported that 11 of 67 patients (16.4%) treated with doses of 66 cobalt-gray equivalents per 10 fractions for hepatocellular carcinoma had rib fractures [18]. APBI may show similar results. Galland-Girodet et al. reported that 4 of 98 patients (4%) treated with three-dimensional conformal APBI using photons with or without electron and proton therapy had rib fractures [19]. Hershko et al. reported that 4 of 21 patients (19%) undergoing APBI with intraoperative electron therapy who did not use lead shielding had rib fractures [20]. Yoshida et al. reported that 2 of 45 Japanese patients (4%) had minor rib fractures, which were healed at the time of the latest follow-up [8].

Smith et al. analyzed the results from 92,735 patients from the SEER-Medicare database, and reported that the rate of rib fracture was significantly higher with brachytherapy (4.5%) than with whole-breast radiotherapy (3.6%) [21]. They did not evaluate the difference between single-channel brachytherapy and multichannel brachytherapy. Huo et al. analyzed the results from 64,112 patients using MarketScan healthcare claims and the Encounters database, and reported that the rate of rib fracture was significantly higher with brachytherapy (1.6%) than with whole-breast radiotherapy (1.3%) [22]. However, the 2,269 patients who received multichannel brachytherapy had a lower rate of rib fracture (1.3%) than the 2,203 patients who received single-channel brachytherapy (1.8%). These results suggest that the outcome of multicatheter interstitial brachytherapy is better than that of single-channel brachytherapy with respect to rib fracture.

To prevent rib fracture, dose-volume analysis may be useful. Many studies have performed dose-volume analyses of the relation between rib fracture and SBRT and proton therapy [17,18,23,24,25,26]. Asai et al. reported that the best predictor of rib fracture from SBRT was the maximum dose ($D_{\text{max}}$) of the rib [24]. Rib fracture occurred in 45.8% of cases when $D_{\text{max}}$ was greater than or equal to 42.4 Gy per four fractions, and in only 1.4% of cases when $D_{\text{max}}$ was less than 42.4 Gy per four fractions. The EQD$_2$ for 42.4 Gy per four fractions was 115.3 Gy. The present study showed that the EQD$_2$ of the fractured rib was 132.9 and 109.5 Gy for $D_{0.01cc}$ and $D_{0.1cc}$, respectively. These results are similar to Asai’s outcomes.

There are few data on DVH of patients undergoing APBI, and this case is now under investigation. Brashears et al. reported that 3 of 105 patients (3%) treated by MammoSite applicator had five ribs fractures. They analyzed the DVH results for these five ribs and found that the maximum doses to 0.1 and 1 cc were 35.4-58.3 and 28.2-45 Gy per 10 fractions, respectively [27]. The present study showed that the $D_{0.1cc}$ and $D_{1cc}$ values of the patient who had a rib fracture were 49.0 and 39.8 Gy per six fractions, respectively. These are also comparable to Brashears’s results.
The relationship between irradiated volume and rib fracture was unknown. However, there is a report that $V_{ref}$, $V_{1.5ref}$, and $V_{2ref}$ were significant risk factors of fat necrosis [28]. In this study, $V_{1.5ref}$ was 34.7 cc although CTV volume was 40 cc. Such high-dose volume may influence rib fracture, although further research is necessary.

From the above discussion, DVH values showing high-dose irradiated volumes ($D_{0.01cc}$, $D_{0.1cc}$, and $D_{1cc}$) seem to be good predictive factors of rib fracture with APBI. However, further investigation is necessary because of the small number of investigated patients.

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Disclosure

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