Care report

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 $D_{0.01cc}$, $D_{0.1cc}$, and D_{1cc} values of the patient were 913, 817, and 664 cGy per fraction, respectively. These values were the highest values in 46 patients. The average $D_{0.01cc}$, $D_{0.1cc}$, and D_{1cc} 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 ($D_{0.01cc}$, $D_{0.1cc}$, and D_{1cc}) 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.

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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

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children as well as for elderly patients or for those who live far from a treatment facility. Recently, a hypofractionation schedule has been tried for WBRT to reduce the treatment time; however, treatment lasting for more than 3 weeks is still necessary [3,4].

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 (V_{ref}), which was the irradiated volume receiving ≥ 100% of the prescribed dose was principally limited to less than 150 cm^3. The dose non-uniformity ratio (DNR), which was defined as $V_{1.5ref}/V_{ref}$ was less than 0.35. $V_{1.5ref}$ 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 ($D_{0.01cc}$, $D_{0.1cc}$, and D_{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_{ref} and $V_{1.5ref}$ were 112 cc and 34.7 cc, respectively, and 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_{90} (CTV) and D_{100} (CTV) were 696 and 614 cGy per fraction, respectively. The $D_{0.01cc}$, $D_{0.1cc}$, and D_{1cc} values of the

Table 1. Patient eligibility criteria

Female invasive/noninvasive ductal/lobular cancer ≤ 3 cm
pN0
cM0
ER positive and/or PR positive
Surgical margin: cancer not exposed
Surgical margin marked with at least 4 clips
No pre-surgical treatment except for hormonal treatment
Age ≥ 35 years
Written informed consent
Performance status: 0 or 1
No collagen vascular diseases except rheumatoid arthritis

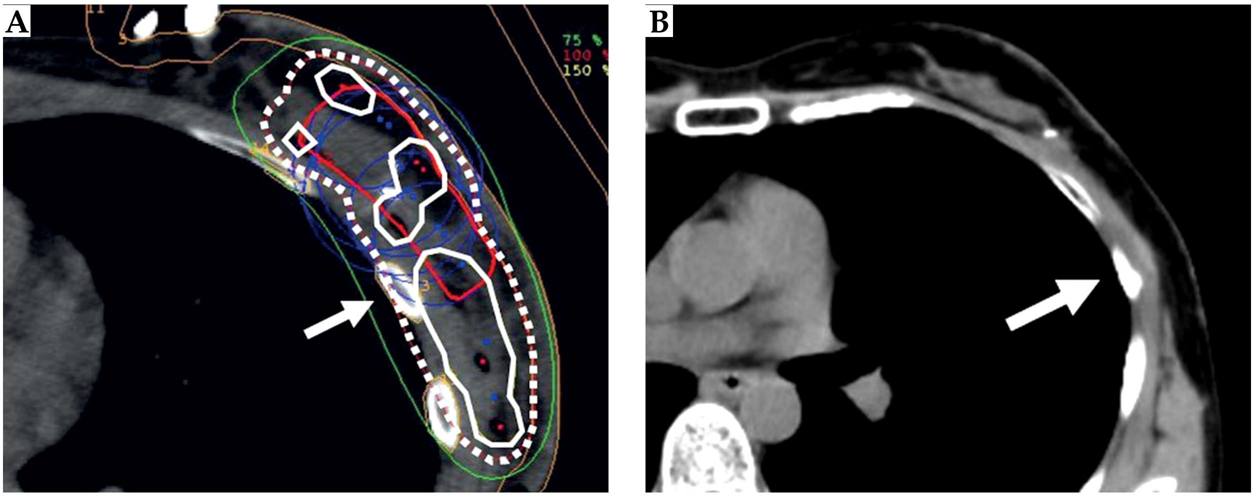

Fig. 1. A) Dose distribution curve of a patient who had a rib fracture as a late complication. The arrow shows the rib that was fractured. White dotted line: 100% prescribed isodose line (36 Gy per six fractions). White solid line: 150% prescribed isodose line (54 Gy per six fractions). Red line: clinical target volume. **B)** Computed tomography image of the patient shown in Figure 1A 11 months after treatment. The arrow shows the rib that was fractured

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_{max}) of the rib [24]. Rib fracture occurred in 45.8% of cases when D_{max} was greater than or equal to 42.4 Gy per four fractions, and in only 1.4% of cases when D_{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.

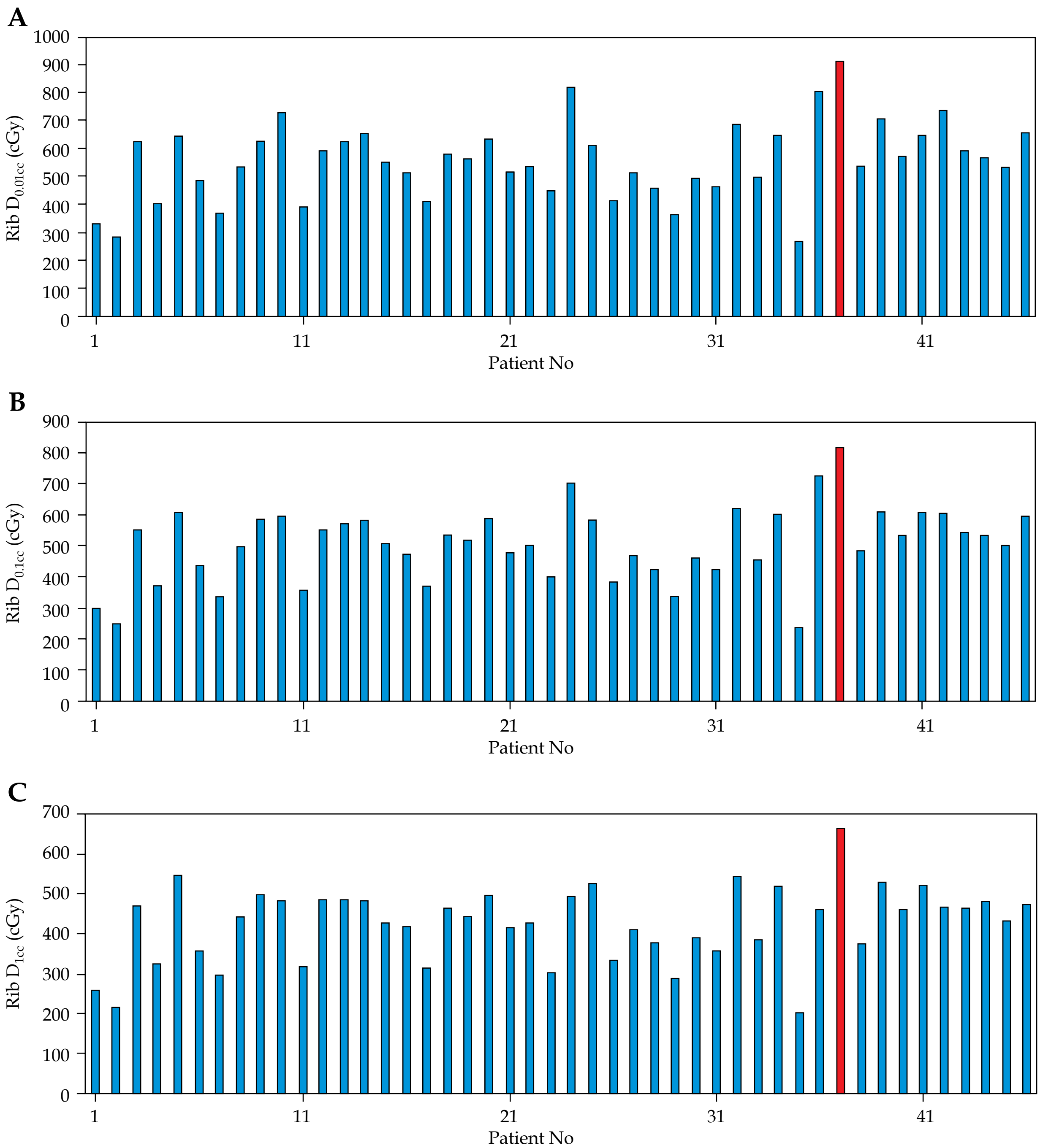

Figure 2. A) $D_{0.01cc}$ values of the rib for all 46 patients. The patient who had a rib fracture was number 37 (red line). The $D_{0.01cc}$ value of the rib was 913 cGy per fraction. **B)** $D_{0.1cc}$ values of the rib for all 46 patients. The patient who had a rib fracture was number 37 (red line). The $D_{0.1cc}$ value of the rib was 817 cGy per fraction. **C)** D_{1cc} values of the rib for all 46 patients. The patient who had a rib fracture was number 37 (red line). The D_{1cc} value of the rib was 664 cGy per fraction

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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References

1. Fisher B, Anderson S, Bryant J et al. Twenty-year follow-up of a randomized trial comparing total mastectomy, lumpectomy, and lumpectomy plus irradiation for the treatment of invasive breast cancer. *N Engl J Med* 2002; 347: 1233-1241.
2. Early Breast Cancer Trialists' Collaborative Group. Favourable and unfavourable effects on long-term survival of radiotherapy for early breast cancer: an overview of the randomised trials. *Lancet* 2000; 355: 1757-1770.
3. Whelan T, MacKenzie R, Julian J et al. Randomized trial of breast irradiation schedules after lumpectomy for women with lymph node-negative breast cancer. *J Natl Cancer Inst* 2002; 94: 1143-1150.
4. Olivotto IA, Weir LM, Kim-Sing C et al. Late cosmetic results of short fractionation for breast conservation. *Radiother Oncol* 1996; 41: 7-13.
5. Latorre JA, Galdós P, Buznego LA et al. Accelerated partial breast irradiation in a single 18 Gy fraction with high-dose-rate brachytherapy: preliminary results. *J Contemp Brachytherapy* 2018; 10: 58-63.
6. Strnad V, Ott OJ, Hildebrandt G et al. 5-Year results of accelerated partial breast irradiation using sole interstitial multicatheter brachytherapy versus whole-breast irradiation with boost after breast-conserving surgery for low-risk invasive and in situ carcinoma of the female breast: a randomised, phase 3, non-inferiority trial. *Lancet* 2016; 387: 229-238.
7. Nose T, Komoike Y, Yoshida K et al. A pilot study of wider use of accelerated partial breast irradiation: intraoperative margin-directed re-excision combined with sole high-dose-rate interstitial brachytherapy. *Breast Cancer* 2006; 13: 289-299.
8. Yoshida K, Nose T, Masuda N et al. Preliminary result of accelerated partial breast irradiation after breast-conserving surgery. *Breast Cancer* 2009; 16: 105-112.
9. Otani Y, Nose T, Dokiya T et al. A Japanese prospective multi-institutional feasibility study on accelerated partial breast irradiation using interstitial brachytherapy: treatment planning and quality assurance. *Radiat Oncol* 2015; 10: 126.
10. Nose T, Otani Y, Asahi S et al. A Japanese prospective multi-institutional feasibility study on accelerated partial breast irradiation using interstitial brachytherapy: clinical results with a median follow-up of 26 months. *Breast Cancer* 2016; 23: 861-868.
11. Yoden E, Nose T, Otani Y et al. Uncertainty of cosmetic evaluation after accelerated partial breast irradiation: interim analysis of a Japanese prospective multi-institutional feasibility study. *Jpn J Radiol* 2017; 35: 381-388.
12. Wadasadawala T, Mondal M, Paul SN et al. Should molecular subtype be recommended as one of the selection criteria for accelerated partial breast irradiation? Preliminary results from an Asian cohort. *J Contemp Brachytherapy* 2018; 10: 47-57.
13. Upreti RR, Budrukkar A, Wadasadawala T. Interobserver variations of target volume delineation and its impact on irradiated volume in accelerated partial breast irradiation with intraoperative interstitial breast implant. *J Contemp Brachytherapy* 2017; 9: 139-145.
14. Major T, Polgár C. Treatment planning for multicatheter interstitial brachytherapy of breast cancer – from Paris system to anatomy-based inverse planning. *J Contemp Brachytherapy* 2017; 9: 89-98.
15. Polgár C, Sulyok Z, Fodor J et al. Sole brachytherapy of the tumor bed after conservative surgery for T1 breast cancer: five-year results of a phase I-II study and initial findings of a randomized phase III trial. *J Surg Oncol* 2002; 80: 121-128.
16. Aliyev JA, Isayev IH, Akbarov KS et al. High-dose-rate interstitial brachytherapy for accelerated partial breast irradiation - trial results of Azerbaijan National Center of Oncology. *J Contemp Brachytherapy* 2017; 9: 106-111.
17. Nambu A, Onishi H, Aoki S et al. Rib fracture after stereotactic radiotherapy for primary lung cancer: prevalence, degree of clinical symptoms, and risk factors. *BMC Cancer* 2013; 13: 68.
18. Kanemoto A, Mizumoto M, Okumura T et al. Dose-volume histogram analysis for risk factors of radiation-induced rib fracture after hypofractionated proton beam therapy for hepatocellular carcinoma. *Acta Oncol* 2013; 52: 538-544.
19. Galland-Girodet S, Pashtan I, MacDonald SM et al. Long-term cosmetic outcomes and toxicities of proton beam therapy compared with photon-based 3-dimensional conformal accelerated partial-breast irradiation: a phase 1 trial. *Int J Radiat Oncol Biol Phys* 2014; 90: 493-500.
20. Hershko D, Abdah-Bortnyak R, Nevelsky A et al. Breast-conserving surgery and intraoperative electron radiotherapy in early breast cancer: experience at the Rambam Health Care Campus. *Isr Med Assoc J* 2012; 14: 550-554.
21. Smith GL, Xu Y, Buchholz TA et al. Association between treatment with brachytherapy vs whole-breast irradiation and subsequent mastectomy, complications, and survival among older women with invasive breast cancer. *JAMA* 2012; 307: 1827-1837.
22. Huo J, Giordano SH, Smith BD et al. Contemporary Toxicity Profile of Breast Brachytherapy Versus External Beam Radiation After Lumpectomy for Breast Cancer. *Int J Radiat Oncol Biol Phys* 2016; 94: 709-718.
23. Pettersson N, Nyman J, Johansson KA. Radiation-induced rib fractures after hypofractionated stereotactic body radiation therapy of non-small cell lung cancer: a dose- and volume-response analysis. *Radiother Oncol* 2009; 91: 360-368.
24. Asai K, Shioyama Y, Nakamura K et al. Radiation-induced rib fractures after hypofractionated stereotactic body radiation therapy: risk factors and dose-volume relationship. *Int J Radiat Oncol Biol Phys* 2012; 84: 768-773.
25. Thibault I, Chiang A, Erler D et al. Predictors of chest wall toxicity after lung stereotactic ablative radiotherapy. *Clin Oncol (R Coll Radiol)* 2016; 28: 28-35.
26. Ishikawa Y, Nakamura T, Kato T et al. Dosemetric parameters predictive of rib fractures after proton beam therapy for early-stage lung cancer. *Tohoku J Exp Med* 2016; 238: 339-345.
27. Brashears JH, Dragun AE, Jenrette JM. Late chest wall toxicity after MammoSite breast brachytherapy. *Brachytherapy* 2009; 8: 19-25.
28. Wazer DE, Lowther D, Boyle T et al. Clinically evident fat necrosis in women treated with high-dose-rate brachytherapy alone for early-stage breast cancer. *Int J Radiat Oncol Biol Phys* 2001; 50: 107-111.