Left breast radiotherapy with multi fields hybrid intensity modulated radiotherapy (IMRT) versus volumetric modulated arc therapy (VMAT) : balance between left anterior descending artery sparing and secondary cancer induction risk

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Abstract

To explore the feasibility of using Volumetric-Modulated Arc Therapy (VMAT) to protect left anterior descending branch (LAD) after breast-conserving surgery for left breast cancer. 15 left breast cancer patients after breast-conserving surgery were selected. 7F-IMRT and 2A-VMAT treatment plans were designed with Varian Eclipse TPS (13.6version). The prescriptions of PTV and PTV Boost were 43.5Gy and 49.5Gy in 15 fractions. The dosimetric parameters, OARs dose sparing and second cancer risk (SCR) were compared between the two plans using a paired t-test. The VMAT plans obtain better PTV conformity and higher mean dose. VMAT plans show a better dose distribution in high dose areas and better sparing of OARs, including left lung, heart, and LAD. The Dmax and Dmean of LAD decreased significantly in VMAT plans. The SCRs of the contralateral lung and breast significantly increased with a higher mean dose. We recommend that contouring and evaluating the dose of LAD and LAD helping structures in left breast cancer radiotherapy. SCR should be evaluated for younger patients.

Keywords: Left breast cancer, radiotherapy, left anterior descending branch, VMAT, second cancer risk
Introduction

Breast cancer was the most frequently diagnosed cancer and the most frequent cause of death from cancer in women. Adjuvant whole-breast radiation therapy following breast-conserving surgery became the main treatment of early invasive breast cancer, for obtaining the same local and regional control rate and long-term survival rate comparing to modified radical mastectomy[1-4]. Hypofractionated dose regimens described equivalent local control, survival, and toxicity to conventional fractionation in published articles[5–8]. Moreover, a simultaneous integrated boost (SIB) of tumor bed has been shown to be more advantageous than sequential boost delivery [9–11].

Non-cancer-related complications may significantly affect the overall survival of breast cancer patients. The study by Colzani et al. [12, 13] assessed the general causes of death in patients with breast cancer in European countries, with the top complications being heart, circulatory, lung, and gastrointestinal diseases, respectively. Many retrospective research had demonstrated a relationship between heart dose and major coronary events. Sarah C et al [14] conducted a population-based case-control study of coronary events in 2168 women who underwent radiotherapy for breast cancer. The rate of major coronary events increased by 7.4% for each increase of 1 Gy in the mean radiation dose delivered to the heart (95% CI, 2.9 to 14.5; P<0.001).

The LAD often located deep into the target area in spatial terms (Figure 1A). The risk of a major coronary event increased linearly with the mean dose to the heart [15,16]. The risk depends on the local radiation dose, which indicated the possibility of reducing the risk by optimizing the dose distribution in the heart and left anterior descending artery (LAD).

The hybrid intensity modulation technique (Hybrid IMRT) [17], which consists of two tangential conformal radiotherapy (CRT) fields and 3-5 IMRT fields, is widespread because of the homogeneous dose distribution and better target coverage comparing to tangential CRT. The volumetric arc modulation radiotherapy (VMAT) technique has been widely used because of its high dose deliver efficiency and OAR sparing. However, the VMAT techniques may increase second cancer risk (SCR) as they involve more beams and a larger exposed normal tissue volume [18,19].
To evaluate the heart and LAD sparing of Hybrid IMRT and VMAT techniques, 15 left-sided whole-breast cancer patients underwent simultaneously integrated boost (SIB) radiotherapy with were selected. Both Hybrid IMRT and VMAT plans were generated. The PTVs dose distribution, OAR sparing and SCR values were evaluated to explore the feasibility of VMAT for whole-breast radiotherapy.

Methods

Ethics approval and consent to participate

The study was approved by the institutional review board of National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital & Shenzhen Hospital. We confirm that all methods were carried out in accordance with relevant guidelines and regulations.

Patient selection and contouring

This study included 15 patients, with median age of 49 years. All the patients were immobilized by a breast bracket in a supine position with upward arms. The CT image with a 5.0 mm slice thickness was acquired using a 16-slice CT scanner (GE Discovery RT, GE Healthcare, Chicago, IL, USA). The clinical target volume (CTV) was contoured to include whole left breast tissue, leaving a 5-mm margin from the skin. The PTV was generated by 5 mm expansion of CTV but cropped 5 mm away from the skin. CTV boost was the 1 cm expansion of tumorbed. PTV Boost was by 5 mm expansion of CTV Boost but within PTV. PTV evaluation was created by separating PTV Boost from PTV. The OARs included Lung L (Ipsilateral lung), Lung R (Contralateral lung), Heart, LAD, LAD PRV 5, LAD PRV 10, Breast R. The LAD PRV 5 and LAD PRV 10 were 5 mm and 1 cm expansion of LAD respectively.

Treatment planning

Both 7F-IMRT (2 CRT + 5 IMRT) and 2A-VMAT plans were generated for each patient using the Varian Eclipse (13.6 Version) treatment planning system (TPS) modeled for the VitalBeam linear accelerator (Varian Medical Systems). The prescribed dose of PTV is 43.5 Gy in 15 fractions (2.9 Gy/fraction). The prescribed dose of PTV Boost is 49.5 Gy in 15 fractions (3.3 Gy/fraction). Table 1 shows the technical parameters of plans.
Table 1 Technique parameters of plans of 15 breast cancer patients underwent radiotherapy

| Plan name | Technique       | Prescribed dose                          |
|-----------|-----------------|------------------------------------------|
| 7F-IMRT   | 2 CRT + 5 IMRT  | 34.8 Gy for CRT plan; 14.7 Gy for IMRT plan |
| 2A-VMAT   | 2Arc VMAT       | 49.5 Gy for 2A-VMAT plan                 |

The 7F-IMRT plan consisted of 2 tangential CRT fields and 5 IMRT fields with fixed gantry angle of 320°, 340°, 30°, 80°, and 110° (Figure 1B). For the 2A-VMAT plan, arc 1 (A1) rotate clockwise from 300° to 160°, and the arc 2 (A2) rotate counterclockwise from from 160° to 300° (Figure 1B). Collimator angles were set at ±5°. Same optimization objective, convolution optimization, and iterative optimization were used.

Figure 1 Beam arrangement of the 7F-IMRT and 2A-VMAT plans used in the study. A) Spatial location of LAD and PTVs. B) Beam arrangement of 7F-IMRT and 2A-VMAT plans. 1) 7F-IMRT plan. The 7F-IMRT plan consisted of 2 tangential CRT fields and 5 IMRT fields with fixed gantry angle of 320°, 340°, 30°, 80°, and 110°. 2) 2A-VMAT plan. A1 rotates clockwise from 300° to 160°, and A2 rotates counterclockwise from 160° to 300°.

Dosimetric evaluation

As to PTV Boost, the 95% dose coverage (D_{95%}), 98% dose coverage (D_{98%}), 2% dose coverage (D_{2%}), PTV Boost mean dose (D_{mean}), homogeneity index (HI), conformity index (CI), Monitor Unit (MU) and Beam on time (BOT) were evaluated. As to PTV, the 95% dose coverage (D_{95%}),
98% dose coverage ($D_{98\%}$), and PTV mean dose ($D_{\text{mean}}$) were evaluated. The HI was defined as:

$$HI = \frac{D_{2\%} - D_{98\%}}{D_p}$$

(1)

The $D_{2\%}$ and $D_{98\%}$ are the doses received by 2% and 98% of the PTV, respectively. $D_p$ is the prescribed dose. The CI was defined as:

$$CI = \frac{V_{t,\text{ref}} \times V_{t,\text{ref}}}{V_t \times V_{\text{ref}}}$$

(2)

$V_{t,\text{ref}}$ is reference isodose (95%) volume within the PTV. $V_t$ is the volume of PTV. The $V_{\text{ref}}$ is the volume of reference isodose (95%).

As to OARs, dose-volume histograms (DVH) were evaluated. The volume of Lung L and heart received 40 Gy ($V_{40}$), 30 Gy ($V_{30}$), 20 Gy ($V_{20}$), 5 Gy ($V_5$) and mean dose ($D_{\text{mean}}$), the volume of LAD, LAD PRV 5 and LAD PRV 10 received 40 Gy ($V_{40}$), 30 Gy ($V_{30}$), 20 Gy ($V_{20}$) and mean dose ($D_{\text{mean}}$), max dose of LAD, LAD PRV 5 and LAD PRV 10, the mean dose ($D_{\text{mean}}$) of Lung R and Breast R were evaluated. The LAD PRV 5 and LAD PRV 10 were expanded 5 mm and 1 cm from LAD.

**Second cancer risk**

The risk of developing a second cancer is usually represented by excess absolute risk EAR (per 10,000 persons-years). Cancer incidence is assumed proportional to the organ equivalent dose (OED). The EAR can be calculated according to

$$\text{EAR} = \text{EAR}_0 \times \text{OED}$$

(3)

The EAR0 (per 10,000 person-years per Gy) for lung and breast cancer incidence at low dose is 7.5 (CI 95: 5.1–10) and 9.2 (CI 95: 6.8–12) cases per 10,000 persons per year per Gy at age of 70 years after exposure at age of 30 years (derived from the A-bomb survivor data) [20]. Thus, the OED is proportional to the second cancer incidence.

We calculated the OEDs of contralateral breast, ipsilateral and contralateral lung were calculated.
for the linear, linear-exponentia, and plateau dose–response models [21,22] based on the
differential DVHs according to

\[
OED_{T,\text{linear}} = \frac{1}{V_T} \sum_i \{DVH(D_i) \cdot D_i \}
\]

(4)

\[
OED_{T,\text{linear–expo}} = \frac{1}{V_T} \sum_i \{DVH(D_i) \cdot D_i \cdot e^{-\alpha D} \}, \alpha=0.044\text{Gy}^{-1}
\]

(5)

\[
OED_{T,\text{plateau}} = \frac{1}{V_T} \{DVH(D_i) \cdot \left(1-e^{-\delta D}\right)/\delta \}, \delta=0.139\text{Gy}^{-1}
\]

(6)

DVH(D_i) is the volume received dose D_i. VT is the volume of summation of all voxels for organ T. 
The α and δ were estimated according to the Japanese A-bomb and Hodgkin cohorts[23].

**Dose delivery**

Total MUs and beam-on time (BOT) of both 7F-IMRT and 2A-VMAT plans were analyzed.

**Statistical analysis**

A paired t-test was performed for 7F-IMRT and 2A-VMAT plans comparison by using SPSS (22
Version).

**Results**

**PTV dose distribution and evaluation**

Figure 2 shows an example of 7F-IMRT and 2A-VMAT plans isodose distributions. Both
7F-IMRT and 2A-VMAT plans could reach clinical constraints. 2A-VMAT plans showed better
conformity with higher CI but a larger volume of low dose coverage. Table 2 summarized the PTV
and PTV Boost dosimetric parameters. As to PTV Boost, 7F-IMRT plans had improved
homogeneity with lower HI, D2%, and Dmean. As to PTV evaluation, the 2A-VMAT plans
achieved higher D2%, D95%, and Dmean.
**Figure 2** An example of 7F-IMRT and 2A-VMAT plans isodose distributions. The green volume represents PTV. The Isodose levels were displayed in Figure 2. A. 7F-IMRT; B. 2A-VMAT.

**Table. 2** Dosimetric comparison results for planning target volumes

| Parameter        | 7F-IMRT         | 2A-VMAT         | P-Value |
|------------------|-----------------|-----------------|---------|
| **PTV Boost**    |                 |                 |         |
| CI               | 0.78±0.08       | 0.80±0.11       | 0.66    |
| HI               | 0.06±0.01       | 0.07±0.01       | 0.02    |
| $D_{2\%}$        | 5224.89±46.59   | 5272.15±43.38   | 0.03    |
| $D_{98\%}$       | 4906.62±21.52   | 4895.79±17.92   | 0.11    |
| $D_{95\%}$       | 4956.25±7.46    | 4954.47±14.14   | 0.37    |
| $D_{mean}$       | 5083.61±25.44   | 5127.45±33.09   | 0.01    |
| **PTV evaluation** |                |                 |         |
| $D_{2\%}$        | 4935.72±59.56   | 4948.36±78.33   | 0.62    |
| $D_{98\%}$       | 4262.81±49.27   | 4235.73±44.19   | 0.12    |
| $D_{95\%}$       | 4362.47±16.33   | 4390.17±156.21  | 0.50    |
Dose sparing of OARs

Tables 3 and 4 summarized OAR dose comparison results of 7F-IMRT and 2A-VMAT plans. The V40, V30, V20, and Dmean of Lung L in 2A-VMAT plans were significantly lower compared to 7F-IMRT plans. The V5 of Lung L is slightly higher. As to heart, 2A-VMAT plans showed significantly improved sparing with lower V40, V30, V20, V5, and Dmean. The Dmean of Lung R and Breast R were higher in 2A-VMAT plans.

Table. 3 Dosimetric comparison results for OARs

| Parameter | 7F-IMRT | 2A-VMAT | P-Value |
|-----------|---------|---------|---------|
| **Lung L** |         |         |         |
| V40       | 6.37±2.69 | 1.09±0.79 | <0.001 |
| V30       | 11.80±3.81 | 6.35±1.85 | <0.001 |
| V20       | 15.06±4.64 | 12.82±2.96 | 0.13 |
| V5        | 41.91±7.79 | 47.73±19.37 | 0.07 |
| Dmean     | 945.63±155.85 | 870.67±112.76 | 0.14 |
| **Heart** |         |         |         |
| V40       | 2.87±1.37 | 0.36±0.54 | <0.001 |
In this study, we aim to compare the LAD sparing of hybrid IMRT and VMAT techniques. LAD and helping structures, including LAD PRV 5 and LAD PRV 10 were contoured. Table 4 summarized the dosimetric comparison results. As to LAD, LAD PRV 5, and LAD PRV 10, the Dmax and volume covered by high isodose levels (V40, V30, and V20) were significantly decreased in 2A-VMAT plans. However, there was no significance in V5. Dmean of LAD, LAD PRV 5, and LAD PRV 10 were significantly lower in 2A-VMAT plans.

Table 4 Dosimetric comparison results for LAD, LAD PRV 5, and LAD PRV 10.
|       | V5         | Dmean     |       |
|-------|------------|-----------|-------|
| 65.62±20.91 | 57.97±21.89 | 0.34     |
| 2602.33±719.16 | 1671.36±554.84 | <0.001  |

**LAD PRV 5**

|       | Dmax      | V40       |       |
|-------|-----------|-----------|-------|
| 4599.45±237.60 | 4271.63±374.19 | 0.008   |
| 50.04±15.45    | 4.94±7.10   | <0.001   |
| 61.47±13.54    | 27.37±15.64 | <0.001   |
| 66.47±13.48    | 45.28±15.46 | <0.001   |
| 71.45±11.72    | 66.39±11.97 | 0.17     |
| 2906.33±470.01 | 1906.98±448.15 | <0.001  |

**LAD PRV 10**

|       | Dmax      | V40       |       |
|-------|-----------|-----------|-------|
| 4744.07±224.86 | 4711.62±221.86 | 0.69    |
| 48.67±13.56    | 14.16±7.79  | <0.001   |
| 63.39±14.06    | 34.61±14.12 | <0.001   |
| 69.04±13.17    | 52.28±15.72 | 0.004    |
| 75.76±9.17     | 69.53±12.78 | 0.14     |
| 3016.27±490.13 | 2177.31±492.74 | <0.001  |

Figure 3 showed the mean dose of heart, LAD, LAD PRV 5, and LAD PRV 10 in 7F-IMRT and 2A-VMAT plans. The dotted line represented the IMRT and VMAT plans had equal values. The results indicated the VMAT plans obtained equal or lower heart mean dose than IMRT plans. VMAT plans acquired significantly lower mean dose of LAD, LAD PRV 5, and LAD PRV 10. VMAT plans had optimized sparing of heart and LAD. The LAD helping structures, such as LAD
PRV5 or LAD PRV 10, could help to evaluate and LAD dose.

Figure 3 Scatter plots showed the mean dose of heart, LAD, LAD PRV 5, and LAD PRV 10 in 7F-IMRT and 2A-VMAT plans. The dotted line represented the the value of IMRT and VMAT plans were equal. The results of 15 cases indicated the VMAT plans obtained equal or lower heart mean dose than IMRT plans. VMAT plans acquired significantly lower mean dose of LAD, LAD PRV 5, and LAD PRV 10.

Figure 4 shows the range of OEDs as calculated by the linear (Fig 4A), linear-exponential (Fig 4B), and plateau (Fig 4C) models for the Lung L, Lung R, Heart, and Breast R. In both 7F-IMRT and 2A-VMAT plans. As to Lung L and heart, 7F-IMRT and 2A-VMAT plans have a similar value of OED. However, as to Lung R and Breast R, the OEDs of 2A-VMAT plans were significantly higher than 7F-IMRT plans. For Lung R, the OEDs increased 133%, 118%, and 246% using linear, linear-exponential, and plateau models. For Breast R, the OEDs increased 168%, 147%, and 321% using linear, linear-exponential, and plateau models.
Figure 4 Organ equivalent doses (OEDs) of Lung L, Lung R, Heart ant Breast R were calculated by linear, linear-exponential, and plateau dose–response models. A) linear; B) linear-exponential; C) plateau.

Discussion
Breast cancer is the most common malignant tumor in women, with more than 1 million new diagnosed each year [24]. Many survivors received adjuvant whole-breast radiation therapy following breast-conserving surgery[1-3]. For left breast cancer, the doses of the heart were usually higher, especially for these patients in whom the distance between the heart to the thoracic wall is small. The risk of a major coronary and other heart diseases increased with the mean dose to the heart. The volumetric arc modulation radiotherapy (VMAT) technique has been widely used because of its high dose deliver efficiency and OAR sparing. Comparing to traditional tangential CRT or hybrid IMRT plans, VMAT plans have a larger coverage volume of low dose, which may increase the second cancer risk (SCR).

In this study, we aim to evaluate the possibility of VMAT techniques for left breast cancer radiotherapy. 15 left breast cancer patients who underwent adjuvant whole-breast radiation were selected. Both hybrid IMRT and VMAT plans were generated for each patient. The PTVs dosimetric characteristics and OARs dose sparing, especially heart, LAD, and LAD helping structures (LAD PRV 5 and LAD PRV 10) were evaluated. Besides, the SCR of both hybrid IMRT and VMAT plans were evaluated.

As to PTV and PTV Boost, both 7F-IMRT and 2A-VMAT plans could reach clinical constraints. VMAT plans showed better conformity but higher mean dose and larger low dose coverage. As to OARs, significantly better dose sparing of contralateral lung, heart, and LAD were observed in VMAT plans. Dmax, Dmean, V40, and V30 of LAD, LAD PRV5, and LAD PRV 10 were significantly decreased in VMAT plans. There is a correlation between heart mean dose and mean dose of LAD, LAD PRV5, and LAD PRV 10.

We evaluated the SCR of the Lungs, heart, and contralateral breast using linear, linear-exponential, and plateau dose-response models based on the differential DVHs. The SCRs of VMAT plans were significantly increased in VMAT plans for the increase of mean dose. Trine G et al found that radiotherapy for breast cancer is associated with an excess risk of second non-breast cancer. For irradiated patients, the incidence of second cancers including the lung, esophagus, thyroid, and connective tissues progressively increased over time.

In this study, hybrid IMRT and VMAT plans were evaluated to explore the possibility of using
VMAT techniques in breast cancer radiotherapy. VMAT plans had better conformity and dose sparing of heart and LAD, but a larger volume of low dose coverage. We recommend that contouring the LAD and LAD helping structures in left breast cancer radiotherapy. SCR should be evaluated for younger patients. The choice of optimal treatment method should be chosen in every patient individually depending on the balance between the cardiac complications and second cancer risks.

Declaration

Author Contributions Statement

Xiaoyong Xiang: Methodology, Data Curation; Writing;

Zhen Ding : Conceptualization, Methodology,

Kailian Kang, Zhitaio Dai, Qi Zeng : Data Curation and preparation of tables;

Meiling Xu, Qingqing Yuan: Preparation of figures;

Wenjue Zhang: Supervision

Ethics approval and consent to participate

The study was approved by the institutional review board of National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital & Shenzhen Hospital. We confirm that all methods were carried out in accordance with relevant guidelines and regulations.

Informed Consent for publication

The informed consents for publication of data have been obtained from patients.

Competing interests

The authors state that they have no competing interests.
References

[1] Siegel RL, Miller KD, Jemal A. Cancer statistics, 2019. CA Cancer J Clin. 2019;69:7-34.

[2] DeSantis C E, Ma J, Goding Sauer A, et al. Breast cancer statistics, 2017, racial disparity in mortality by state[J]. CA: a cancer journal for clinicians, 2017, 67(6): 439-448.

[3] Kohler B A, Sherman R L, Howlader N, et al. Annual report to the nation on the status of cancer, 1975-2011, featuring incidence of breast cancer subtypes by race/ethnicity, poverty, and state[J]. JNCI: Journal of the National Cancer Institute, 2015, 107(6).

[4] Colzani E, Liljegren A, Johansson A L V, et al. Prognosis of patients with breast cancer: causes of death and effects of time since diagnosis, age, and tumor characteristics[J]. Journal of Clinical Oncology, 2011, 29(30): 4014-4021.

[5] Dellas K, Vonthein R, Zimmer J, et al. Hypofractionation with simultaneous integrated boost for early breast cancer[J]. Strahlentherapie Und Onkologie, 2014, 190(7): 646-653.

[6] Haviland J S, Owen J R, Dewar J A, et al. The UK Standardisation of Breast Radiotherapy (START) trials of radiotherapy hypofractionation for treatment of early breast cancer: 10-year follow-up results of two randomised controlled trials[J]. The lancet oncology, 2013, 14(11): 1086-1094.

[7] Whelan T J, Pignol J P, Levine M N, et al. Long-term results of hypofractionated radiation therapy for breast cancer[J]. New England Journal of Medicine, 2010, 362(6): 513-520.

[8] James M L, Lehman M, Hider P N, et al. Fraction size in radiation treatment for breast conservation in early breast cancer[J]. Cochrane Database of Systematic Reviews, 2010 (11).

[9] Alford S L, Prassas G N, Vogeleas C R, et al. Adjuvant breast radiotherapy using a simultaneous integrated boost: clinical and dosimetric perspectives[J]. Journal of medical imaging and radiation oncology, 2013, 57(2): 222-229.

[10] Van Parijs H, Reynders T, Heuninckx K, et al. Breast conserving treatment for breast cancer: dosimetric comparison of different non-invasive techniques for additional boost delivery[J]. Radiation Oncology, 2014, 9(1): 36.
[11] Bantema-Joppe E J, Vredeveld E J, de Bock G H, et al. Five year outcomes of hypofractionated simultaneous integrated boost irradiation in breast conserving therapy; patterns of recurrence[J]. Radiotherapy and oncology, 2013, 108(2): 269-272.

[12] Colzani E, Liljegren A, Johansson A L V, et al. Prognosis of patients with breast cancer: causes of death and effects of time since diagnosis, age, and tumor characteristics[J]. Journal of Clinical Oncology, 2011, 29(30): 4014-4021.

[13] Afifi A M, Saad A M, Al-Husseini M J, et al. Causes of death after breast cancer diagnosis: A US population-based analysis[J]. Cancer, 2019.

[14] Darby SC, Ewertz M, McGale P, et al. Risk of ischemic heart disease in women after radiotherapy for breast cancer. N Engl J Med. 2013;368(11):987-998.

[15] Chang JS, Shin J, Park EC, Kim YB. Risk of cardiac disease after adjuvant radiation therapy among breast cancer survivors. Breast. 2019;43:48-54.

[16] Jacobse JN, Duane FK, Boekel NB, et al. Radiation Dose-Response for Risk of Myocardial Infarction in Breast Cancer Survivors. Int J Radiat Oncol Biol Phys. 2019;103(3):595-604.

[17] Smith W, Menon G, Wolfe N, Ploquin N, Trotter T, Pudney D. IMRT for the breast: a comparison of tangential planning techniques. Phys Med Biol. 2010;55(4):1231-1241.

[18] Karpf D, Sakka M, Metzger M, Grabenbauer GG. Left breast irradiation with tangential intensity modulated radiotherapy (t-IMRT) versus tangential volumetric modulated arc therapy (t-VMAT): trade-offs between secondary cancer induction risk and optimal target coverage. Radiat Oncol. 2019;14(1):156.

[19] Dumane VA, Saksornchai K, Zhou Y, Hong L, Powell S, Ho AY. Reduction in low-dose to normal tissue with the addition of deep inspiration breath hold (DIBH) to volumetric modulated arc therapy (VMAT) in breast cancer patients with implant reconstruction receiving regional nodal irradiation. Radiat Oncol. 2018;13(1):187.

[20] Preston DL, Ron E, Tokuoka S, et al. Solid Cancer Incidence in atomic bomb survivors: 1958–1998. Radiat Res 2007;168:1–64.
[21] Zwahlen DR, Ruben JD, Jones P, Gagliardi F, Millar JL, Schneider U. Effect of intensity-modulated pelvic radiotherapy on second cancer risk in the postoperative treatment of endometrial and cervical cancer. Int J Radiat Oncol Biol Phys 2009;74:539–45.

[22] Schneider U, Zwahlen D, Ross D, Kaser-Hotz B. Estimation of radiation-induced cancer from three-dimensional dose distributions: concept of organ equivalent dose. Int J Radiat Oncol Biol Phys 2005;61:1510–5.

[23] Zwahlen DR, Ruben JD, Jones P, Gagliardi F, Millar JL, Schneider U. Effect of intensity-modulated pelvic radiotherapy on second cancer risk in the postoperative treatment of endometrial and cervical cancer. Int J Radiat Oncol Biol Phys 2009;74:539–45.

[24] Ferlay J, Shin HR, Bray F, Forman D, Mathers C, Parkin DM. GLOBOCAN 2008, v1.2, cancer incidence and mortality worldwide: IARC CancerBase No. 10. Lyon, France: International Agency for Research