JBUON 2021; 26(3): 753-758
ISSN: 1107-0625, online ISSN: 2241-6293 • www.jbuon.com
Email: editorial_office@jbuon.com

ORIGINAL ARTICLE

Comparative analysis of the absorbed dose in the heart and anterior descending branch of the left coronary artery (LAD) in patients with left-sided breast cancer who received radiotherapy using 3D-CRT, IMRT and VMAT techniques

Tamara Kuzba-Kryszak[1], Sławomir Nowakowski[2], Janusz Winiecki[2,3], Roman Makarewicz[3,4]

[1]Radiotherapy Department, Oncology Center in Bydgoszcz, Poland. [2]Medical Physics Department, Oncology Center in Bydgoszcz, Poland. [3]Chair, Clinic of Oncology and Brachytherapy, Collegium Medicum in Bydgoszcz, Nicolaus Copernicus University in Torun, Poland. [4]Brachytherapy Department, Oncology Center in Bydgoszcz, Poland.

Summary

Purpose: *The purpose of this study was to compare the absorbed dose distributions within the heart and lad in patients with left-sided breast cancer who underwent radiotherapy using 3D-CRT, IMRT and VMAT techniques.*

Methods: *The treatment plans of 11 patients with left-sided breast cancer were analyzed. All of the patients were irradiated in our facility with DIBH 3D-CRT. For all patients the plans in the IMRT (sliding window) and VMAT (Rapid Arc – Varian) techniques were prepared. Cumulative dose-volume histograms (DVH) were used to compare the dose distributions between the plans for each patient. Statistical analysis was carried out using the one-way ANOVA with repeated measurements and Tukey's post hoc test.*

Results: *The use of IMRT and VMAT techniques allowed for a better coverage of the PTV with 95% isodose and a more homogeneous dose distribution compared to the 3D-CRT technique. The use of dynamic technique (IMRT or VMAT) did not provide significant protection for OARs - only the dose absorbed in LAD was slightly lower.*

Conclusion: *The use of 3D-CRT allows better protection of critical organs compared to other techniques, except for the dose in the lad artery which was the lowest in IMRT technique. exposure of large tissue volumes to so-called low radiation doses is undoubtedly a disadvantage of using dynamic techniques.*

Key words: *breast radiation therapy, dose-volume histogram, mean heart dose, radiation therapy techniques, dose-to-lad artery*

Introduction

The incidence of breast cancer in Europe is still increasing. In Poland, the incidence of breast cancer has more than doubled over the past three decades. Breast cancer is the biggest oncological problem in developed countries [1]. However, the prognosis of these patients has improved with the use of new drugs, new radiotherapy techniques and improvement of surgical treatment techniques. Fortunately, the proportion of patients diagnosed in the early stages of disease is increasing. This means that the survival of breast cancer patients and number of patients after oncological treatment also increase. All this make the prevention of cardiotoxicity (the most severe and worrying side effect) very necessary [2,3].

A very important factor that determines the risk of the so-called cardiac events after radiation therapy for breast or the chest wall (after mastec-

Corresponding author: Janusz Winiecki, PhD. Head of Medical Physics Department, Oncology Centre in Bydgoszcz
ul. dr Izabeli Romanowskiej 2, 85-796 Bydgoszcz, Poland.
Tel: +48 52 3743090, Email: janusz@co.bydgoszcz.pl
Received: 31/10/2020; Accepted: 16/12/2021

tomy), are the dose delivered to the heart and the dose delivered to the anterior descending branch of the left coronary artery (LAD) [4-6]. According to a population-based study a 1 Gy reduction in the average dose deposited in the heart contributes to a 7.4% decrease in the risk of heart disease [7]. However, it has not been established whether there is a dose below which the risk of cardiotoxicity is abolished. According to EBCTCG, the risk of death as a result of cardiotoxicity after radiotherapy within 15 years after treatment is 1.27 [8]. It was also found that as many as 90% of deaths not related to breast cancer were deaths due to heart disease in these patients [9].

Many studies have shown that the dose deposited in the heart during radiation therapy for the left breast is much higher than for the right one. This means that patients with left breast cancer treated with radiotherapy have a higher risk of dying from cardiac causes than the others [10-14]. Techniques for reducing the risk of side effects have been intensively sought for many years. Today, much attention is paid to the quality of life of patients after oncological treatment, because the role of radiotherapy in reducing the risk of local and regional recurrence is well known and well-established.

The techniques that lead to dose reduction in organs at risk (OAR) (including heart and LAD) are: irradiation in prone positioning, proton beam therapy, Intensity Modulated Radiation Therapy (IMRT), Deep Inspiratory Breath Hold (DIBH), partial breast irradiation and intraoperative (electron beam) radiotherapy (IOeRT) [15]. However, all of these treatments have their limitations and they cannot be used in all patients. The choice of technique that effectively reduces the dose in OAR must take into account: the patient's anatomy, stage, cancer subtype, age and comorbidities.The DIBH method seems to be the most promising because it can be used in most patients [16-19]. However, some studies show that the use of IMRT or VMAT (volumetric modulated arc therapy) techniques can also contribute to better protection of OAR such as the heart or LAD artery compared to the commonly used 3D conformal technique (3D CRT-3D conformal radiotherapy) [16,20-22], although some researchers report that better protection for OAR in 3D-CRT plans have been obtained [23,24]. All authors admit (irrespective of the effectiveness of OAR protection) that IMRT and VMAT techniques allow for a more homogeneous dose distribution in the planning target volume (PTV) area and its better coverage with 95% isodose.

The aim of this study was to compare the absorbed dose distributions within the heart and anterior descending branch of the left coronary artery (LAD) in patients with left-sided breast cancer who underwent radiotherapy using 3D-CRT, IMRT and VMAT techniques.

Methods

The treatment plans of 11 patients with left-sided breast cancer were analysed. All of the patients were irradiated in our facility with DIBH 3D-CRT. Respiration monitoring was carried out using the Real-Time Position Management system (RPM, Varian Medical Systems). Computed tomography for treatment planning was performed in such a way that the distance between cross-sections was 3mm. The clinical target volume (CTV), the planning target volume (PTV) region, lungs, spinal cord, heart, LAD and opposite breast were contoured at each slice. The left breast was usually irradiated using 2 or 4 tangential photon beams with 6MV and 15MV nominal accelerating potential (NAP). The geometry of the plan was not only to minimize the dose in the heart, but also

Table 1. Patient characteristics

Patient no.	*TNM*	*Bolus*	*PTV volume (cm^3)*	*CTV volume (cm^3)*	*Heart volume (cm^3)*	*LAD volume (cm^3)*
1	T1cN0M0	Yes	1194	933	554	5.8
2	T1cN0M0	No	693	475	527	4.5
3	T1cN0M0	Yes	1227	949	528	35
4	T2N0M0	Yes	1052	772	651	4.5
5	T2N0M0	Yes	1168	891	391	3.1
6	T1bN0M0	No	2758	2338	749	4.3
7	T2N0M0	Yes	1527	1142	662	4.9
8	T1cN0M0	Yes	730	488	488	4.6
9	T2N0M0	No	819	613	540	3.6
10	T1cN0M0	No	1221	938	558	6.2
11	T1cN0M0	Yes	911	633	611	8.6

to protect the other breast. A total dose of 42.5 Gy in 17 fractions per PTV area was assigned to all patients, and the ICRU requirement had to be met (the dose had to be in the range of 95-107%). Except of external beams radiotherapy, the tumor bed received an additional 10 Gy using brachytherapy. The characteristics of patients are given in Table 1.

In the next step, for all patients the plans in the IMRT (sliding window) and VMAT (Rapid Arc – Varian) techniques were prepared. In the IMRT technique, 5 to 7 coplanar 6MV or 15MV beams were used. In the VMAT technique, the number of arcs was from 2 to 5 and the NAP was 6MV. Cumulative dose-volume histograms (DVH) were used to compare the dose distributions between the plans for each patient. In particular, the dose the absorbed by the heart and LAD was analysed. Statistical analysis was carried out using the One Way ANOVA with repeated measurements and Tukey's *post hoc* test. Statistical analysis was carried out using the one-way ANOVA with repeated measurements and Tukey's *post hoc* test. The use of the ANOVA method was aimed at indicating the irradiation method which gave results significantly different from other irradiation techniques. The parameters compared were PTV coverage by 95% isodose, the minimum dose in the PTV and homogeneity index.

Results

The 95% isodose covered 97.82%, 98.66%, 98.19% of the PTV area in 3D-CRT, IMRT and VMAT, respectively. This means that the IMRT technique has gained a slight advantage over the other irradiation techniques. The average minimum dose in the PTV area was 83.7%, 82.6%, 84.6% for plans in these techniques, respectively. The most homogeneous dose distribution was obtained in the VMAT plans: mean homogeneity index (HI) 0.22 vs 0.26 for 3D and 0.25 for IMRT.

The IMRT technique is characterized by a significant increase in irradiation time, which undoubtedly affects the comfort of patients and carries the risk of intra-fractional mobility. The realisation of the treatment plan requires 3-5 times more monitor units in this case as compared to other techniques. The values of minimum doses, maximum doses, number of monitor units and values of homogeneity index are given in Table 2.

The use of 3D-CRT allows better protection of critical organs compared to other techniques, except for the dose in the LAD artery (Table 3). Regarding cardiac parameters - mean dose, V25 and V30, the lowest values were obtained in 3D-CRT plans. The differences between the values in the 3D and IMRT plans did not reach statistical significance, while these values were significantly higher in the VMAT vs 3D vs IMRT plans (Figure 1). Statistical analysis was carried out using the

Table 2. Treatment plans characteristics

Patient no.	D_{min} (%) *3D-CRT*	D_{min} (%) *IMRT*	D_{min} (%) *VMAT*	D_{max} (%) *3D-CRT*	D_{max} (%) *IMRT*	D_{max} (%) *VMAT*	*Monitor Units 3D-CRT*	*Monitor Units IMRT*	*Monitor Units VMAT*	*Homog. Index 3D-CRT*	*Homog. Index IMT*	*Homog. Index VMAT*
1	86.3	90.1	91.1	109.3	106.3	108.8	413.1	1436.9	685.3	0.22	0.16	0.17
2	88.2	68.8	86.3	108.8	106.8	108.2	369.8	1375.4	550.7	0.20	0.37	0.21
3	73.2	71.7	79.1	108.8	110.9	105.4	306.0	1848.1	597.4	0.35	0.39	0.26
4	84.9	83.7	87.0	109.7	104.6	106.1	409.2	1535.5	364.9	0.24	0.20	0.19
5	86.9	90.2	88.0	108.9	104.5	106.0	295.6	1292.1	413.0	0.22	0.14	0.18
6	81.2	85.2	80.4	110.5	113.7	109.4	291.0	2107.8	376.0	0.29	0.28	0.29
7	88.0	78.8	79.5	109.9	106.6	107.9	274.0	1462.3	587.3	0.22	0.28	0.28
8	87.6	86.3	90.3	109.7	107.2	105.7	300.7	1432.1	483.8	0.22	0.21	0.15
9	83.8	84.9	86.0	109.8	108.6	106.0	398.4	1542.9	721.3	0.26	0.24	0.20
10	72.5	85.6	75.8	110.6	107.8	105.9	334.5	2084.8	820.0	0.38	0.22	0.30
11	88.5	83.4	86.9	109.5	107.3	105.5	357.7	1668.3	503.9	0.21	0.24	0.18

D_{min}: minimum dose expressed in % as a percentage of the set dose. D_{max}: maximum dose in %.

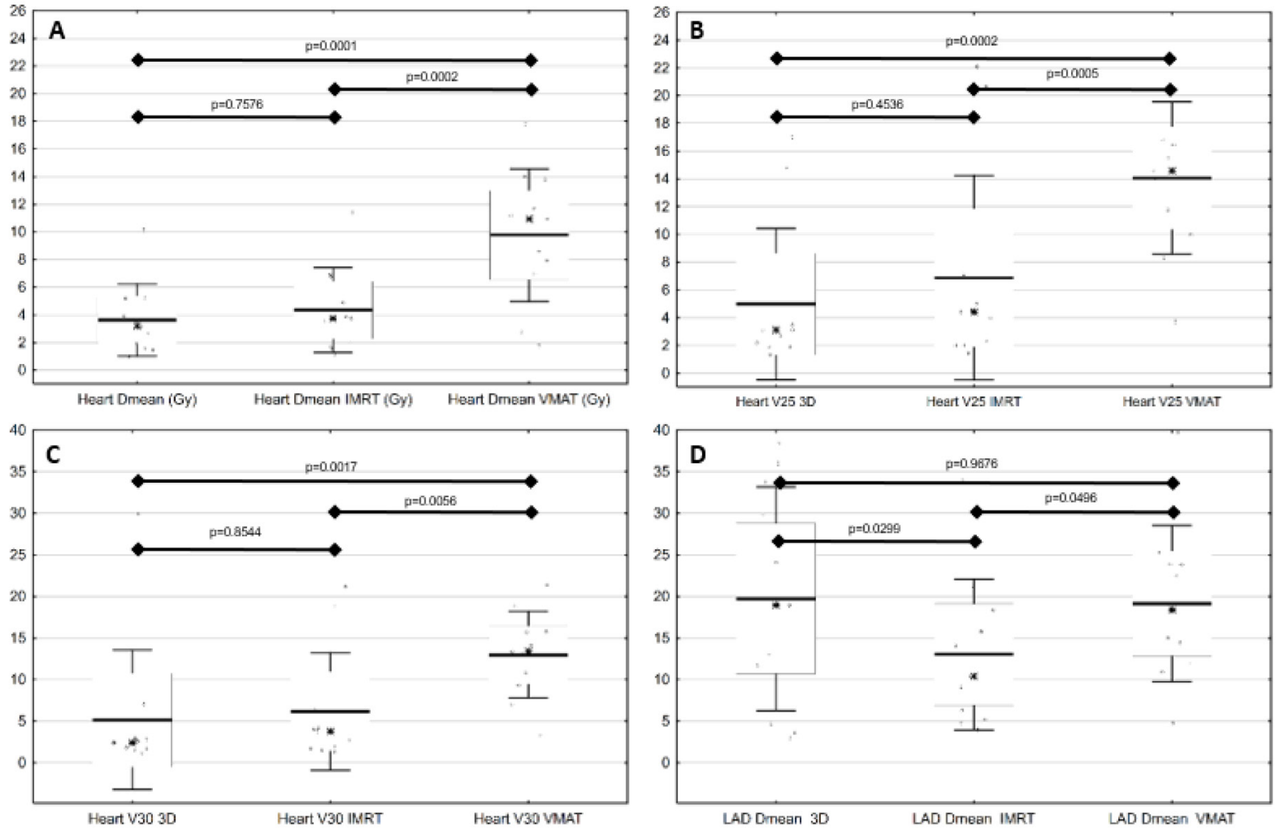

Figure 1. Comparison of average doses (Gy) for the heart **(A)**, V25 **(B)**, V30 **(C)** and **(D)** for LAD. Data expressed as mean (line), median (star), SD (bars), and interquartile range (box), and individual data points (dots).

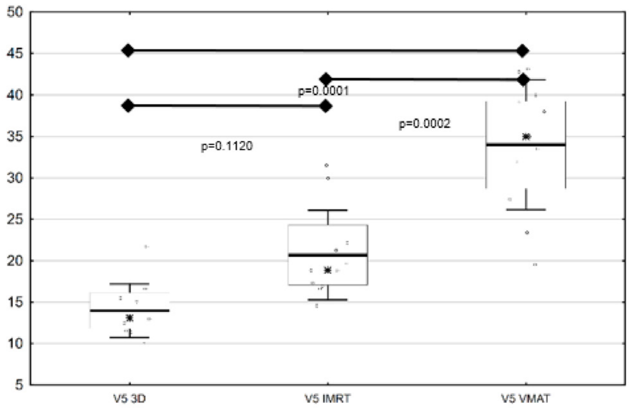

Figure 2. Comparison of the V5 parameter in the analyzed treatment plans. Data expressed as mean (line), median (star), SD (bars), and interquartile range (box), and individual data points (dots).

one way ANOVA with repeated measurements and Tukey's *post hoc* test.

Exposure of large tissue volumes to so-called low radiation doses is undoubtedly a disadvantage of using dynamic techniques in left breast radiotherapy. The study adopted the V5 parameter, i.e. the volume receiving the 5Gy dose. Figure 2 presents a graph illustrating the differences in these volumes for the compared irradiation techniques.

Table 3. Dose distribution analysis

Technique: *Volume*	*3D-CRT*	*IMRT*	*VMAT*
Heart Dmean (Gy)	3.620	4.35	9.77
Heart V25	4.990	6.88	14.06
Heart V30	5.130	6.16	13.96
LAD Dmean (Gy)	19.72	13.00	19.13
Left lung V20	16.01	21.26	27.06
Both lungs V20	6.880	8.73	13.59
Right breast (Gy)	0.730	0.66	4.94
V5	13.96	20.69	33.99

Discussion

IMRT has an established role in irradiating patients with prostate and H&N cancers. Some studies also show the benefit of using this technique in patients with breast cancer (reduction of the dose deposited within the heart) [16,25], but other studies do not confirm this [24,26]. The use of IMRT and VMAT techniques allows for a better coverage of the PTV area with 95% isodose and a more homogeneous dose distribution compared to the 3D-CRT technique [20,22,25] , which is confirmed in the treatment plans analysed in this work. The use of dynamic technique (IMRT or VMAT) did not provide significant protection for OARs - only the dose absorbed in LAD was slightly lower (Table 3).

Particular caution should be taken when assessing the average dose within the heart, as 2 treatment plans with the same average dose may significantly differ in dose distribution in this structure. In dynamic techniques, larger volumes of the heart are exposed to low radiation doses, while high doses are usually deposited in a small volume. While the long-term consequences of high doses for the heart are well known (studies on patients treated with radiation therapy for lymphomas located in the mediastinum) [27-31], the long-term adverse effects of low doses are not yet known. In addition, due to the very diverse structure and physiology of the heart, the assessment of average doses in the entire organ seems to be insufficient.

Sarah et al [18] compared treatment plans for patients with left-sided breast cancer using 3D-CRT and VMAT (RapidArc) on free breathing and on hold of inspiration (DIBH). A similar coverage of the PTV area with 95% isodose was obtained for both methods. The VMAT technique resulted in a more homogeneous dose distribution and a lower dose within the left lung volume and within the sum of the volumes of both lungs. When analyzing the average dose for the heart, it was observed that if the average dose in the 3D-CRT-DIBH plan exceeded 3.2Gy, then in the VMAT plans a noticeable reduction of this parameter was achieved. In the other patients this effect was not observed and the dose in VMAT was higher than in 3D-CRT. The use of the VMAT technique was associated with a significant increase in the average dose in the right breast area, which certainly limits the use of this technique in younger patients [18].

The fear of widespread use of IMRT and VMAT techniques for the treatment of patients with left-sided breast cancer is the exposure of significant body volume to low radiation doses, usually in the range of 5-10% of the planned dose.

In their work, Abo-Madyan et al [32] estimated and compared the risk of secondary solid tumors in patients irradiated due to breast cancer using the 3D-CRT technique, IMRT using tangential fields, classic IMRT multi-field and WMAT-ARC Therapy. The obtained results indicate a significantly lower risk of inducing a secondary tumour after the application of 3D-CRT and IMRT techniques from tangential fields compared to IMRT multi-field and VMAT. The difference is even 50% depending on the calculation model used [32]. Factors particularly affecting the risk of secondary cancer in this group of patients include systemic treatment, lifestyle and genetic loads. Especially in young patients, this risk should be considered.

Comparison of the analysed radiotherapy techniques in patients with breast cancer is difficult because most reports in the literature relate to small groups of patients, and these are only dosimetric comparisons. When planning radiation therapy, one should strive to limit the maximum volume of the heart in the radiation field, without giving up the appropriate dose in the target (PTV) area. A heart-safe radiation dose has not yet been established.

Conflict of interests

The authors declare no conflict of interests.

References

1. Wojciechowska U, Didkowska J. Illnesses and deaths from malignant neoplasms in Poland. National Registry of Cancer, National Institute of Oncology, available ON http://onkologia.org.pl/raporty/
2. Darby S, McGale P, Correa C. Effect of radiotherapy after breast-conserving surgery on 10-year recurrence and 15-year breast cancer death: meta-analysis of individual patient data for 10,801 women in 17 randomised trials. Lancet 2011;378:1707-16.
3. Adamska AJ. The problem of cardiotoxicity of radiotherapy in breast cancer. Lett Oncol Sci 2017;14:16-21. https://doi.org/10.21641/los.14.1.26
4. Taylor CW, Nisbet A, McGale P. Cardiac exposures in breast cancer radiotherapy: 1950s-1990s. Int J Radiat Oncol Biol Phys 2007;69:1484-95.
5. Taylor CW, Povall JM, McGale P. Cardiac dose from contemporary tangential breast cancer radiotherapy in the year 2006. Int J Radiat Oncol Biol Phys 2008;72: 501-7.
6. Nieder C, Schil S, Kneschaure K. Influence of different treatment techniques on radiation dose to the LAD coronary artery. Radiat Oncol 2007-2:20.
7. Darby SC, Ewertz M, McGale P. Risk of ischemic heart disease in women after radiotherapy for breast cancer. N Engl J Med 2013;368:987-98. doi: 10.1056/NEJMoa1209825.
8. EBCTCG - Early Breast Cancer Trialists' Collaborating Group, Effects of radiotherapy and of differences in the extent of surgery for early breast can. J Clin Oncol 1994;12:447-53.

9. Bartlett FR, Yarnold JR, Kirby AM. Breast radiotherapy and heart disease - where are we now? Clin Oncol 2013;25:687-9.
10. Darby SC, McGale P, Taylor CW. Long-term mortality from heart disease and lung cancer after radiotherapy for early breast cancer: prospective cohort study of about 300,000 women in US SEER cancer registries. Lancet Oncol 2005;6:557-65.
11. Giordano SH, Kuo YF, Freeman JL Risk of cardiac death after adjuvant radiotherapy for breast cancer. J Natl Cancer Inst 2005;97:419-24.
12. Wang W, Wainstein R, Freixa X. Quantitative coronary angiography findings of patients who received previous breast radiotherapy. Radiother Oncol 2011;100:184-8.
13. Harris EE, Correa C, Hwang WT. Late cardiac mortality and morbidity in early-stage breast cancer patients after breast-conservation treatment. J Clin Oncol 2006;24:4100-6.
14. Roychoudhuri R, Robinson D, Putcha V. Increased cardiovascular mortality more than fifteen years after radiotherapy for breast cancer: a population-based study. BMC Cancer 2007;7:9.
15. Chan TY, Tang JI, Tan PW. Dosimetric evaluation and systematic review of radiation therapy techniques for early stage node-negative breast cancer treatment. Cancer Manag Res 2018;10:4853-70.
16. Shah C, Badiyan S, Berry S. Cardiac dose sparing and avoidance techniques in breast cancer radiotherapy. Radiother Oncol 2014;112:9-16.
17. Remouchamps, VM, Vicini FA, Sharpe MB. Significant reductions in heart and lung doses using deep inspiration breath hold with active breathing control and intensity-modulated radiation therapy for patients treated with locoregional breast irradiation. J Radiat Oncol Biol Phys 2003; 55:392-406.
18. Osman S, Hol S, Poortmans P. Volumetric modulated arc therapy and breath-hold in image-guided locoregional left-sided breast irradiation. Radiother Oncol 2014;112:17-22.
19. Nissen HD, Appelt AL. Improved heart, lung and target dose with deep inspiration breath hold in a large clinical series of breast cancer patients. Radiother Oncol 2013;106:28-32.
20. Zhu Q, Kirova YM, Cao L. Cardiotoxicity associated with radiotherapy in breast cancer: A question-based review with current literatures. Cancer Treat Rev 2018;68: 9-15.
21. Osman SO, Hol S, Poortmans PM: Volumetric modulated arc therapy and breath-hold in image-guided locoregional left-sided breast irradiation. Radiother Oncol 2014;112:17-22.
22. Lauche O, Kirova YM, Fenoglietto P. Helical tomotherapy and volumetric modulated arc therapy: New therapeutic arms in the breast cancer radiotherapy. World J Radiol 2016;8:735-42.
23. Schubert LK, Gondi V, Sengbusch E. Dosimetric comparison of left-sided whole breast irradiation 3DCRT, forward-planned IMRT, inverse-planned IMRT, helical tomotherapy, and topotherapy. Radiother Oncol 2011;100:241-6.
24. Mężeński P, Gałecki J, Zawadzka A. Comparison of 3D-CRT and IMRT methods in the irradiation of breast cancer patients after conserving surgery without and with the inclusion of supraclavicular-axillary lymph nodes. J Oncol 2012;62:423-30.
25. Korczyńska BS, Śladowska A, Bogusz BR. Comparison between intensity modulated radiotherapy (IMRT) and 3D tangential beams technique used in patients with early-stage breast cancer who received breast-conserving therapy. Rep Pract Oncol Radiother 2010;15:79-86.
26. Badakhshi H, Kaul D, Nadobny J. Image-guided volumetric modulated arc therapy for breast cancer: a feasibility study and plan comparison with three-dimensional conformal and intensity-modulated radiotherapy. Br J Radiol 2013;86:20130515.
27. Madan R, Benson R, Sharma DN: Radiation induced heart disease: Pathogenesis, management and review literature. J Egypt Natl Canc Inst 2015;27:187-93.
28. Aleman BM, van den Belt-Dusebout AW, Klokman WJ. Long-term cause-specific mortality of patients treated for Hodgkin's disease. J Clin Oncol 2003;21:3431-9.
29. Hoppe RT: Hodgkin's disease: complications of therapy and excess mortality. Ann Oncol 1997;8 (Suppl 1):115-8.
30. Ng AK, Bernardo MP, Weller E. Long-term survival and competing causes of death in patients with early-stage Hodgkin's disease treated at age 50 or younger. J Clin Oncol 2002;20:2101-8.
31. Swerdlow AJ, Higgins CD, Smith P. Myocardial infarction mortality risk after treatment for Hodgkin disease: a collaborative British cohort study. J Natl Cancer Inst 2007;99:206-14.
32. Abo-Madyan Y, Aziz MH, Aly MM. Second cancer risk after 3D-CRT, IMRT and VMAT for breast cancer. Radiother Oncol 2014;110:471-6.