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Deep inspiration breath-hold radiotherapy for left-sided breast cancer after conserving surgery: A dose reduction for organs at risk

Radioterapija karcinoma leve dojke pri zadržanom dahu u dubokom udisaju nakon konzervacione hirurgije: smanjenje doze na organe u riziku

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Abstract

Background/Aim. For patients with left-sided breast cancer, a major concern is the dose of radiation delivered to the heart, because of increased risk of exposure and consequently increased risk of major coronary events and side effects. In order to reduce the dose to the heart during breast irradiation, deep inspiration breath-hold (DIBH) technique was implemented in our institution. The aim of this retrospective study was to compare dosimetric parameters of DIBH on the heart, left anterior descending artery (LAD) and ipsilateral lung (IL), compared with free breathing (FB) technique. **Methods.** Twenty patients who underwent radiotherapy with DIBH at our institution were retrospectively analyzed. Two computed tomography (CT) scans were acquired for each patient, FB-CT and DIBH-CT. Plans consisted of two opposed tangential segmented beams and one direct beam with small dose contribution. Doses to the heart, LAD, and IL were assessed. **Results.** Dosimetric comparison between FB and DIBH for mean dose to the heart was 5.17 Gy vs. 3.68 Gy, respectively ($p < 0.0001$), and the mean percentage of the volume receiving 25 Gy was 4.63% vs. 0.85%, respectively ($p < 0.0001$). Mean dose for LAD was 26.09 Gy vs. 11.89 Gy, respectively ($p = 0.00014$). Mean percentage of the volume receiving 20 Gy for the IL was 15.16% vs. 13.26% ($p = 0.0007$) for FB and DIBH, respectively. **Conclusion.** Implementation of DIBH technique in radiotherapy treatment of patients with left-sided breast cancer statistically significantly reduces the dose delivered to the surrounding organs at risk, particularly to the heart and LAD, with optimal target coverage.

Key words:
breast neoplasms; postoperative period; radiotherapy; respiration; heart; lung.

Apstrakt

Uvod/Cilj. Za bolesnice sa dijagnozom karcinoma lijeve dojke, značajan problem predstavlja doza koju će primiti srce, te povišen rizik od koronarne bolesti srca i drugih neželjenih efekata. Kako bi smanjili dozu na srce tokom zračenja tangencijalnim poljima, implementirana je *deep inspiration breath-hold* (DIBH) tehnika u našem radioterapijskom centru. Cilj ove retrospektivne studije bio je poređenje dozimetrijskih parametara DIBH tehnike na srce, levu prednju descendentnu arteriju (LAD) i ipsilateralno plućno krilo (IL), u odnosu na radioterapijski tretman tokom slobodnog disanja. **Metode.** Retrospektivno je analizirano dvadeset bolesnica koje su ozračene DIBH tehnikom u našem radioterapijskom centru. Za svaku bolesnicu napravljene su dvije serije kompjuterizovane tomografije, jedna tokom slobodnog disanja i druga za DIBH tehniku. Planovi su se sastojali od dva tangencijalna segmentna polja i jednog direktnog polja sa malim doprinosom doze. Urađena je komparacija doze na organe od rizika: srce, LAD i IL. **Rezultati.** Izmerena vrednost srednje doze na srce između slobodnog disanja i DIBH tehnike bila je 5,17 Gy i 3,68 Gy, redom ($p < 0,0001$), dok je srednja procentna vrednost volumena koji prima 25 Gy bila 4,63% i 0,85%, redom ($p < 0,0001$). Srednja doza na LAD je iznosila 26,09 Gy i 11,89 Gy, redom ($p = 0,00014$). Srednja procentna vrednost volumena IL koji prima 20 Gy bila je 15,16% i 13,26%, redom ($p = 0,0007$). **Zaključak.** Uvođenje DIBH tehnike u radioterapijski tretman kod bolesnica sa karcinomom lijeve dojke statistički značajno smanjuje dozu koju će primiti okolni organi od rizika, naročito srce i LAD, uz optimalnu pokrivenost ciljnog volumena.

Ključne reči:
dojka, neoplazme; postoperativni period; radioterapija; disanje; srce; pluća.

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Introduction

Breast cancer is the most common malignant disease in the female population. The estimated number of new breast cancer cases worldwide during 2012 was 1,676,600 and the estimated number of breast cancer deaths was 521,900. Breast cancer is the most frequent cause of death from malignant diseases in female population in less developed countries, and the second one in more developed countries [1].

Radiotherapy significantly improves local control rates and an overall survival for patients with early breast cancer, who previously underwent the breast conserving surgery [2]. Effects on the heart constitute a potentially significant and serious clinical problem in radiation therapy of early breast cancer. Increased cardiac mortality among irradiated patients may compromise potential benefit in terms of a reduced risk of recurrence or death from breast cancer [3]. Radiation exposure of the heart can lead to coronary artery disease, congestive heart failure, valvular heart disease, pericardial disease, conduction abnormalities and sudden cardiac death [4]. In combination with systemic therapy, anthracyclines and trastuzumab, it may increase the risk of cardiac toxicity [5]. The heart and left anterior descending artery (LAD) exposure during breast cancer radiotherapy, increases the subsequent rate of the ischemic heart disease. The increase is proportional to the mean dose to the heart. It begins within a few years after the exposure and continues for at least 20 years [6].

In a conventional radiotherapy (RT) technique, scan is taken with the patient in the treatment position, but without taking breathing motion into account. Different techniques were developed in order to decrease radiation dose to the heart during breast cancer treatment. Deep inspiration breath-hold (DIBH) radiotherapy is a promising one. In deep inspiration there is separation between target and organs at risk: the heart and LAD. That is basic concept for introduction of DIBH in left breast cancer treatment. The goal is to reduce dose to the heart and LAD by delivering radiation only in the breathing phase in which the anatomical position of organs of risk and target is optimal. In the breath-hold technique, the respiratory phase, during which irradiation is delivered, is selected as the most favorable in terms of distance between the target volume and the organs at risk. Respiratory gating allows the radiation beam to be turned on and off whenever patient moves in and out of a planned position (which is usually close to the maximal inspiration) [7, 8].

In the studies of Lin et al. [9] and Hong et al. [10] one can find dose reduction for the heart and LAD during breathing adopted radiotherapy of left breast cancer but in this study, we also evaluated doses for the ipsilateral lung (IL) and contralateral breast.

Other studies [11–13], using modern techniques such as intensity modulated radiation therapy (IMRT), volumetric modulated arc therapy (VMAT) or tomotherapy for breast cancer treatment, showed that there is an advantage of field in field (FIF) DIBH technique over IMRT, VMAT and tomotherapy, which reduces the maximum dose and increases lower dose regions and the mean dose to organs at risk.

The primary aim of this study was to determine and compare dose distributions to the heart, LAD and ipsilateral lung (IL) during adjuvant left-sided breast cancer radiotherapy with DIBH and free breathing (FB) technique. Doses to clinical target volume (CTV) and planning target volume (PTV) and contralateral breast were also assessed and compared.

Methods

Patient selection

In the period from January 2015 to October 2017, 20 patients referred for adjuvant RT after left breast cancer preserving surgery were treated in our institution with DIBH technique using Real-Time Positioning Management (RPM) system (Varian Medical Systems, Palo Alto, CA, USA) [14]. Patients with left-sided breast cancer with negative regional nodes after breast conserving surgery were candidates for this study. Generally, only patients who could reproduce a breath-hold, were included.

Methodology

All patients went through educational sessions with a radiation therapist, who introduced them with DIBH technique. They were coached to hold breath at the same inhale respiratory phase for at least 15 seconds.

Data acquisition

FB and DIBH computed tomography (CT) series (2.5 mm slice thickness) were made for all patients in supine position with arms above their head (immobilization – the All-In-One breast and lung board solution – Orfit Industries Wijnegem, Belgium), on a GE Lightspeed CT (General Electric Medical Systems, Waukesha, WI) equipped with the RPM system. The RPM Respiratory Gating technology enables correlation of the target position with the patient's respiratory cycle [14]. An infrared tracking (Charged-Couple Device – CCD) camera mounted in the room for CT simulation and in the tretment room was used with a reflective marker usually placed over the xiphoid process. Position was marked on patient's skin so it could easily be reproduced during the whole treatment process. The system measures the patient's respiratory pattern and range of motion and displayes them as a waveform [14]. After precise determination of the target volume movement in relation to the waveform, gating thresholds were set along the waveform, in order to mark the target volume in the desired portion of the respiratory cycle [14]. These thresholds determined when the automatic gating system should turn the treatment beam on and off on the LINAC. We used audio and visual guidance during the treatment.

Delineation

For breast-conserving operations, CTV was delineated according to the Radiation Therapy Oncology Group (RTOG) consensus guidelines [15]. Contouring of organs at risk was performed in accordance with the guidelines published by the RTOG [16].

PTV was made separately in FB-CT and DIBH-CT, for plan evaluation. PTV was generated using a 8 mm and 7 mm margin from CTV for FB and DIBH, respectively, limited to the midline, and shrunk 4 mm from the skin. The ipsilateral lung was contoured using an automatic contouring tool.

The LAD coronary artery was delineated in the anterior interventricular groove from its initiation down to the apex of the heart. Delineation was done according to the CT-based cardiac atlas by Feng et al. [17]. In order to reduce the interobserver variability, the same physician delineated LAD for each patient. Target volumes were checked by an experienced radiation oncologist. Only non-contrast CT scans were used, because intravenously contrast enhanced CT scans did not improve the delineation accuracy [18].

Treatment planning and dose constraints

Field-in-field RT technique were performed on DIBH and FB CT series with two opposed tangential medial-lateral segmented beams and one direct beam (with dose weight < 10%). The prescribed dose was 50 Gy in 25 fractions. The energy of the beams was 6 MV, and the fields were shaped with Varian Millennium 120 multileaf collimator. Treatment planning was performed with the Varian Eclipse 10.0 treatment planning system (TPS) and calculated with Anisotropic Analytical Algorithm (AAA). Dose variation between +7% and 5% was accepted in PTV following ICRU 50 and 62. Dose–volume histograms were extracted and compared for each of DIBH and FB plans. For PTV we determined coverage of 95% of PTV and mean dose. For the heart, the volume covered with 25 Gy (V25) as well as the mean heart dose were measured. For the IL, the volume covered with 20 Gy (V20) was analysed. For the LAD, the mean dose was analyzed. For the contralateral breast we compared volume receiving 5Gy and 10Gy (V5 and V10, respectively).

Before the first fraction, it was mandatory to perform the treatment plan dosimetry verification by MapCHECK2 (SunNuclear, Melbourne, FL) device. The criteria was that 95% of the pixels pass with a 3% dose tolerance of reference values and a distance to agreement (DTA) 3 mm (gamma: 3%, 3 mm).

Statisticaly analysis

Paired-samples Student's *t*-test (2-tailed hypothesis test) was used for statistical analysis of the comparison of PTV and CTV dose coverage but for the organs at risk we used Wilcoxon 2-tailed test because distribution of data for organs at risk was not normal and standard deviation was big. We have tested normality of distribution with SPSS statistical software version 23.0. Data were considered statistically significant at $p < 0.05$.

Results

The mean age ± standard deviation (SD) of the observed twenty patients was 47 ± 7.2 years (range 34–60 years. In Table 1 we presented comparision of mean doses in Gy for the heart and LAD during FB and DIBH.

Result of the volume dose constraint for organ at risk – the heart (V25) for FB was 4.63%, and for DIBH 0.85% ($p = 0.000089$), with a decrease of 81.6% (Figure 1). The mean heart dose for FB was 5.17 Gy vs. 3.68 Gy for DIBH ($p < 0.0001$), with a decrease of 28.8%.

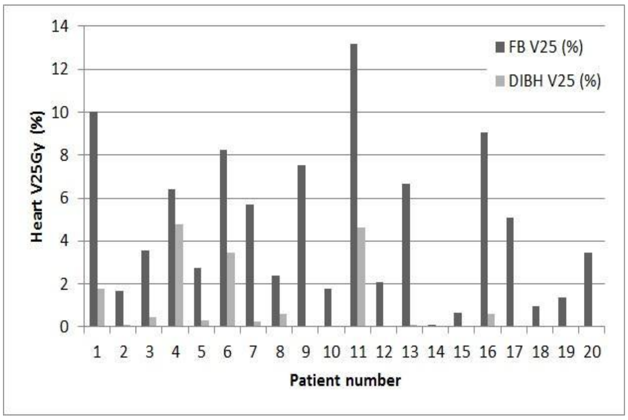

Fig. 1 – Heart V25 in % values for free breathing (FB) vs. deep inspiration breath hold (DIBH) for all 20 patients. V25 – the volume covered with 25 Gy.

In comparison with FB, the mean dose delivered to LAD was decreased for 54% if DIBH technique was used (26.09 Gy vs. 11.88 Gy, respectively; $p = 0.00014$) (Figure 2).

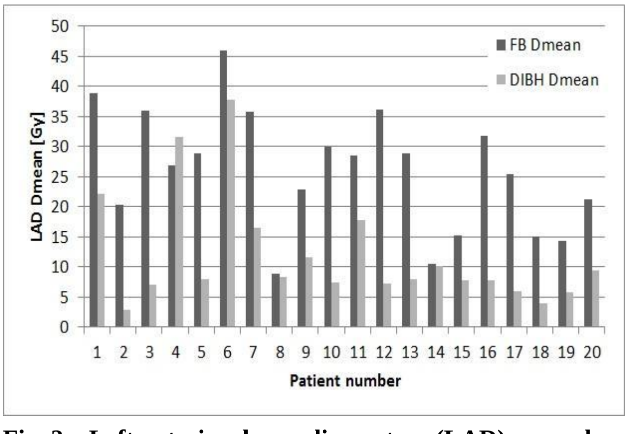

Fig. 2 – Left anterior descending artery (LAD) mean dose in Gy for free breathing (FB) and deep inspiration breath hold (DIBH) for all 20 patients.

Result of the volume dose constraint for organ at risk – the IL (V20) was 15.16% vs. 13.26% for FB and DIBH, respectively ($p = 0.04$) (Figure 3). The volume was decreased by 144.73 cm^3 (42.8%) with FB compared to DIBH technique.

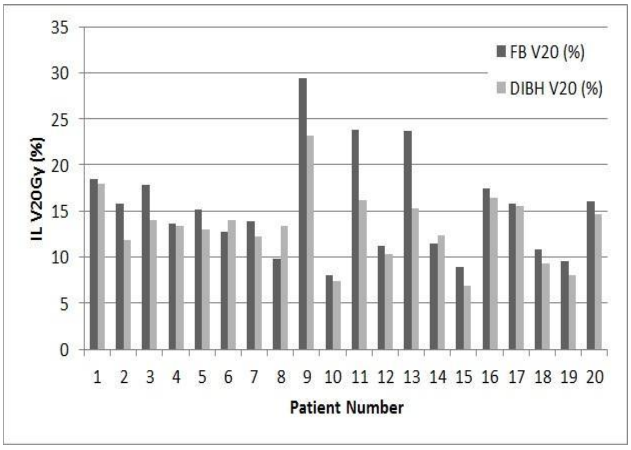

Fig. 3 – Comparison between free breathing (FB) and deep inspiration breath hold (DIBH) for ipsilateral lung (IL) V20 in %, for all 20 patients.
V25 – the volume covered with 20 Gy.

Usually a small volume of the right breast was exposed and the comparison between FB and DIBH for V5 was 1.20% vs. 0.81%, ($p = 0.157$) and for V10, it was 0.87% vs. 0.49% ($p = 0.133$), respectively (Figure 4).

The mean 95% coverage of PTV for FB and DIBH plans was 96.58% vs. 96.33%, respectively ($p = 0.186$). Mean coverage value for 95% of CTV was 98.13% for FB vs. 97.85% for DIBH ($p = 0.297$).

A survey of mean irradiation doses for the heart and LAD during FB and DIBH used in this and earlier published studies is given in Table 1.

Discussion

The heart dose parameters were significantly reduced in the present study. It is directly related to the position-distance from the chest wall and the relative curvature of the anterior chest wall, size and position of the breast, etc. [19]. The published results of the left-sided breast cancer radiotherapy indicate reduction of the irradiated heart and LAD volumes, although there were no literature data available to correlate a given risk of cardiac complication [20, 21].

Based on QUANTEC, the heart V25 value should be less than 10%, with probability of cardiac mortality less than 1% [22]. The heart V25 values for FB and DIBH in this study

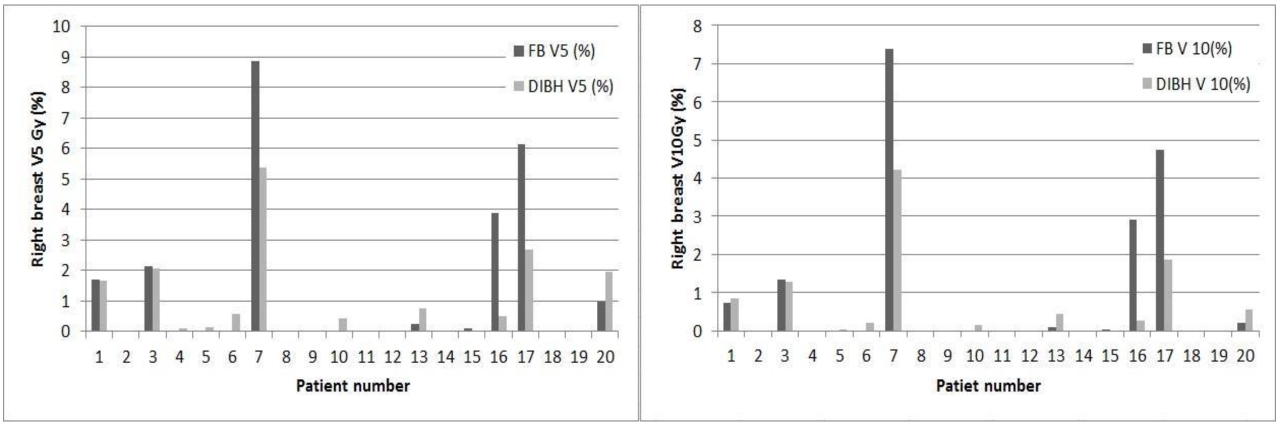

Fig. 4 – The comparison of free breathing (FB) and deep inspiration breath hold (DIBH) for the right breast, V5 and V10 in %.
V5 and V10 – the volume covered with 5 Gy and 10 Gy, respectively.

Table 1
Survey of mean irradiation doses (Dmean) for the heart and left anterior descending artery (LAD) during free breathing (FB) and deep inspiration breath-hold (DIBH) used in different studies

Study	Heart (Dmean), Gy		LAD (Dmean), Gy	
	FB	DIBH	FB	DIBH
Bruzzaniti et al.[20]	1.68	1.24	9.01	2.74
Vikström J et al.[24]	3.7	1.7	18.1	6.4
Hjelstuen et al.[25]	6.2	3.1	25	10.9
Wang W et al.[27]	3.17	1.32	20.47	5.94
Lee HY et al.[28]	4.53	2.52	26.26	16.01
Lin A et al.[9]	1.41	0.82	12.24	4.25
Joo et al.[29]	7.24	2.79	40.79	23.69
Rochet N et al.[30]	2.5	0.9	14.9	4.0
Hayden AJ et al.[31]	6.9	3.9	31.7	21.9
Bolukbasi Y et al.[32]	1.74	0.66	1.71	0.78
This study	5.17	3.68	26.09	11.88

and the studies of Yeung et al. [23] (0.8% vs 0.1%, respectively), Vikstrom et al. [24] (2.0% vs 0.0%, respectively) and Hjelstuen et al. [25] (6.7% vs 1.2%, respectively), had a similar volume reduction. DIBH technique also showed better result for the heart V25 compared to that of a study of Fan et al. [26] (7.89%) for patients treated in FB prone position.

Clinical evaluation and comparison of mean heart doses and LAD doses are very important, because cardiac toxicity due to radiation therapy has a prolonged latency period. Patients with breast cancer and good prognostic factors have a long life expectancy, and it is very important to reduce potential acute and late side effects due to radiation therapy of breast cancer. DIBH is promising technique in terms of reduced cardiac morbidity and mortality. In several studies, DIBH has been associated with significant improvement in both mean heart doses and mean LAD doses, when comparing the same patients planned with FB and DIBH [9, 20, 24, 25, 27–32].

Retrospective data from a large analysis of both community and academic centers demonstrates that patients treated with DIBH had an average lower heart doses than those treated with FB [10].

In this study, all patients had dosimetric benefit from DIBH technique, in terms of cardiopulmonary dose reduction. However, the mean dose to LAD exceeded 20 Gy in case of three patients. This result was related to the position-distance of the LAD from the chest wall and the curvature of the anterior chest wall. Position of the breast and understanding of coaching during CT simulation were also reasons for higher doses to the LAD.

Using DIBH technique the same target dose coverage was achieved compared to FB technique.

The relatively small sample size was a limitation to this study because the achievement of DIBH criteria was not possible for all patients. Patient coaching before CT simulation was necessary but also time consuming [33].

The strength of this study was using exactly the same patient cohort in both DIBH and FB plans.

Negative side of the use of DIBH technique is increased radiotherapy treatment room workflow due to a complex set-up procedure. Treatment time is also increased when several breath-holds are needed to complete the irradiation of a beam, therefore we are using maximal dose rate to decrease the beam-on time.

Secondary malignancies related to radiation are a problem in breast cancer patients. In this study, there was no significant difference in contralateral breast doses between DIBH and FB plans. This was also demonstrated by Johansen et al. [34]. Relative risk estimates for secondary contralateral breast cancer are almost the same either using DIBH or FB technique. If modern radiotherapy techniques are in use for breast cancer irradiation, one should carefully evaluate the region of lower doses in contralateral breast.

Conclusion

DIBH radiotherapy of left-sided breast cancer, utilizing audio and video guidance, statistically significantly reduces radiation doses to the heart and LAD without compromising target coverage. More effort should be given to patient coaching before CT simulation because it is the only factor that is not anatomy related and can result in lower doses to the heart and LAD.

Future research should be done in the field of precise dose constraints determination for cardiac specific tissues (pericardial tissue, valves, etc.) and to find out prediction factors that point out the patients with highest benefit from DIBH technique.

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