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ORIGINAL ARTICLE / ОРИГИНАЛНИ РАД

Left breast radiotherapy – the impact of heart and left anterior descending artery doses to cardiovascular diseases developed eight years after treatment

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SUMMARY

Introduction/Objective Left breast cancer patients undergoing radiotherapy are at higher risk of cardiovascular diseases (CVD), as a partial volume of the heart is anatomically close to target volume. This may cause CVD in the years following cancer treatment.

The aim of this work was to develop a scoring system which identifies patients with increased risk of development of CVD, as a consequence of the left breast irradiation.

Methods The patients followed up in this study were treated during 2009. Eight years later, they were invited to participate in a study where they underwent a cardiology evaluation. Their current condition was statistically correlated to the doses received by their heart and left anterior descendant artery (LAD).

Results Out of 114 patients, 31 women were evaluable for cardiology assessment. Out of these 31 subjects, six women were with a history of CVD before cancer treatment. Four women never developed any kind of heart associated disease, while in the other 27, newly onset CVD were diagnosed ranging from hypertension to myocardial infarction, strongly positively correlated to doses to heart and LAD ($p = 0.003$). Severity of developed cardiovascular toxicity was formulated through the correlation of mean heart and mean LAD doses with CVD developed in the form of a scoring system.

Conclusion The doses to critical organs depend on patient anatomy and technique of irradiation. The cardiovascular complications are proven as consequence of radiotherapy. Scoring system based on doses received by heart and LAD is a reliable tool in predicting CVD.

Keywords: cardiotoxicity; computer-assisted radiotherapy planning; left-sided breast cancer; radiotherapy

INTRODUCTION

Breast cancer is a global health care problem worldwide and in the Republic of Serbia: 26% of all new cancer cases in Serbian female population were breast cancer patients, where approximately half of them are left-breast patients [1, 2].

Cardiovascular diseases (CVD) are the first cause of death worldwide according to the World Health Organization. Together, malignant and CVD are the cause of 3/4 of all deaths (both sexes, all ages) in Serbia, where CVD are responsible for 52.1% and cancer for 22.8% of all deaths [3]. Incidences of both diseases are rising.

Radiation therapy of the breast is known to contribute to CVD, and has been reported as a possible cause of cardiac mortality since 1950s [4].

Due to increased reporting on correlation between cancer therapy and CVD, the European Society of Cardiology and International Atomic Energy Agency have published documents on the cardiovascular toxic effect of cancer therapy, including radiotherapy and chemotherapy summarizing evidence [5, 6]. Increase in number of patients receiving chemotherapy and radiotherapy, earlier detection of disease and longer survival, lead to an increase in the number of new patients in cardiology, and may pose a global future problem.

The implementation of modern radiation therapy techniques has significantly lowered the dose to the heart and to the left descending coronary artery (LAD) both often very close to target volume. The usual doses to these two structures are far above 0.5 Gy, stated as limit in International Commission on Radiological Protection (ICRP 118).

The objective was to assess the toxic effect to these structures in our patient set, from radiotherapy aspect. The constraints given in the literature were very limited, so we conducted a retrospective analysis of treatment plans and patient conditions, to determine scoring system based on threshold values of mean heart dose (MHD) and mean LAD (MLAD) dose that would have clinical significance for development of CVDs.

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METHODS

The subjects were patients with left breast cancer treated during 2009. The Radiotherapy department of our Institute was equipped at that time with two linear accelerators, by Varian Medical Systems, Clinac series (Palo Alto, CA, USA). The computed tomography simulator was manufactured by Siemens (Munich, Germany). The treatment planning system XIO used was manufactured by Computerized Medical Systems (nowadays Elekta, Stockholm, Sweden), and the dose was calculated by the convolution algorithm. Treatment plans were generated using a 6 MV beam, which was verified according to the International Atomic Energy Agency recommendations [7, 8].

The treatment planning strategy at that time was two opposed tangential fields with enhanced dynamic wedges, and sub-fields [9].

Patients were immobilized on the Wing board® (Civco, Coralville, IO, USA) or Thorawedge® (Civco). Radiation oncologists delineated the target volume (breast), both lungs, and the heart. The LAD was not delineated at the time of treatment. Dose prescribed to the center of the breast (The International Commission on Radiation Units and Measurements reference point) was 50–60 Gy, with or without boost and supraclavicular lymph nodes, depending on the type and stage of the disease. Treatment plans were evaluated based on dose volume histograms. Patient position was verified before the first fraction on a portal imaging device and then checked weekly.

The patients in this study were invited eight years after cancer treatment, to a clinical cardiological examination. Out of the 114 patients invited, 31 attended examinations, while others either did not answer, or members of the family reported their death (three patients). Out of the subset of 31 women who responded to the cardiology examination and finally entered the study, 27 women were confirmed with CVD and only four women had never had any kind of CVD.

Patient's cardiology assessment consisted of a physical examination, an electrocardiogram, an echocardiography, an exercise stress test and included further diagnostic and therapeutic procedures. echocardiography evaluated atherosclerotic changes of aortic walls, aortic valves, left atrium dimension and volume; mitral valve; left ventricle walls and dimension, systolic (ejection fraction) and diastolic function; cavities of the right heart and systolic pressure and systolic function of the right ventricle; pulmonary artery and valve as well as pericardium. The stress tests were conducted for patients with symptoms of coronary artery disease or an irregular heart rhythm (arrhythmia). The overall conclusion of cardiologist for each patient was included in data analysis.

At the time of treatment planning in 2009, the LAD artery was not contoured. Since LAD cannot be visualized reliably on computed tomography images made for treatment planning, radiation oncologists delineated the LAD structure on the de-archived plans according to guidelines and clinical atlases, and the heart [10, 11]. The physicists re-calculated treatment plans by the clinical version of the treatment planning system XIO (Elekta) to obtain doses to these two new structures (heart and LAD).

Figures were generated by the software Origin Pro 8.0 (Northampton, MA, USA).

The patients at the hospital are treated according to the approved clinical radiation therapy protocols, by the Ethical board. Every patient signed approval for their treatment, and the cardiological study was purely volunteered. Patients examined by cardiologists got their cardiologist report, and also signed approval before any treatment was initiated based on findings from this study.

RESULTS

The patients were identified from the hospital registry, with their clinical data.

There was in total 114 left breast cancer patients irradiated during 2009, of which 92 could be successfully de-archived seven years after treatment, and returned to the treatment planning system, without any errors during the de-archiving procedure. Out of this number, 86 patients could be recalculated without an error in the treatment planning system. Six plans had unknown calculation error. Finally, 31 patients responded to the appointment with cardiologist at the time when study was conducted and were included in dose/CVD evaluation.

At the time of the treatment, age distribution was as follows: there were no patients younger than 30 and older than 80. Four patients (3.5%) of 114 patients were in their 30s, 28% of patients in their 40s, 30.7% patients in their 50s, 34.3% patients in their 60s and 3.5% of patients in their 70s.The mean age of female left breast patients during the year 2009 was 60.9 years.

The distribution of diagnosis was as follows: most of the 114 patients had ductal carcinoma (55.3%), medullar carcinoma was present in 4.4% patients, lobular carcinoma in 9.6%, mixed type in 3.5%, tubular, micropapillary and mucinous in 0.9%. In 28 patients (24.6%) there were no data on the type of carcinoma.

When the tumor grade was evaluated in the group, there were 11% of patients with G1 grade, 28% of patients with G2 grade, 13% of patients with G3 grade, while no data was present for 52% of the patients.

There were no records in the hospital database about CVD risk factors associated with heart diseases prior to cancer treatment.

The chemotherapy drugs before, during and after radiation therapy were: 32% patients received two drug combination, mainly FAC and tamoxifen, 6% received three drugs, 0.9% had four drugs, while one drug was received by 32% of patients, mainly tamoxifen; 3.5% did not have chemotherapy at all, while there was no data for 24.5% of the patients in the system (most likely received chemotherapy in local hospitals). The chemotherapy agents used were as follows: fluorouracil, doxorubicin, cyclophosphamide; adriamycin and cyclophosphamide; cyclophosphamide, methotrexate, fluorouracil, tamoxifen, docetaxel, paclitaxel, bevacizumab, trastuzumab, goserelin. All medicines listed

Table 1. Doses to heart, LAD, and left lungs (min., max., and mean dose per patient and per cardiologically assessed cohort)

Mean dose range of heart (Gy)	Number of patients	Heart				LAD				Left lung			
		Avg. of mean dose (Gy)	Avg. of min. dose (Gy)	Avg. of max. dose (Gy)	Avg. volume (cm^3)	Avg. of mean dose (Gy)	Avg. of min. dose (Gy)	Avg. of max. dose (Gy)	Avg. volume (cm^3)	Avg. of mean dose (Gy)	Avg. of min. dose (Gy)	Avg. of max. dose (Gy)	Avg. volume (cm^3)
0–2 Gy	7	1.58	0.18	46.92	654.2	8.92	0.72	33.22	4.73	4.88	0.05	59.46	1321.42
2–4 Gy	8	3.07	0.27	55.94	708.9	21.56	0.95	53.97	5.23	6.22	0.11	60.46	1172.63
4–6 Gy	8	4.92	0.32	55.8	652.13	25.39	1.18	55.11	4.42	8.03	0.18	60.71	1208.6
6–14 Gy	8	8.82	0.7	56.6	897.4	30.57	2.77	55.65	6.34	8.02	0.3	57.9	1176.8
Data for all patients	31	4.6	0.37	53.81	727.17	21.63	1.4	49.49	5.18	6.78	0.16	59.63	1219.8

Avg. – average; LAD – left anterior descending artery

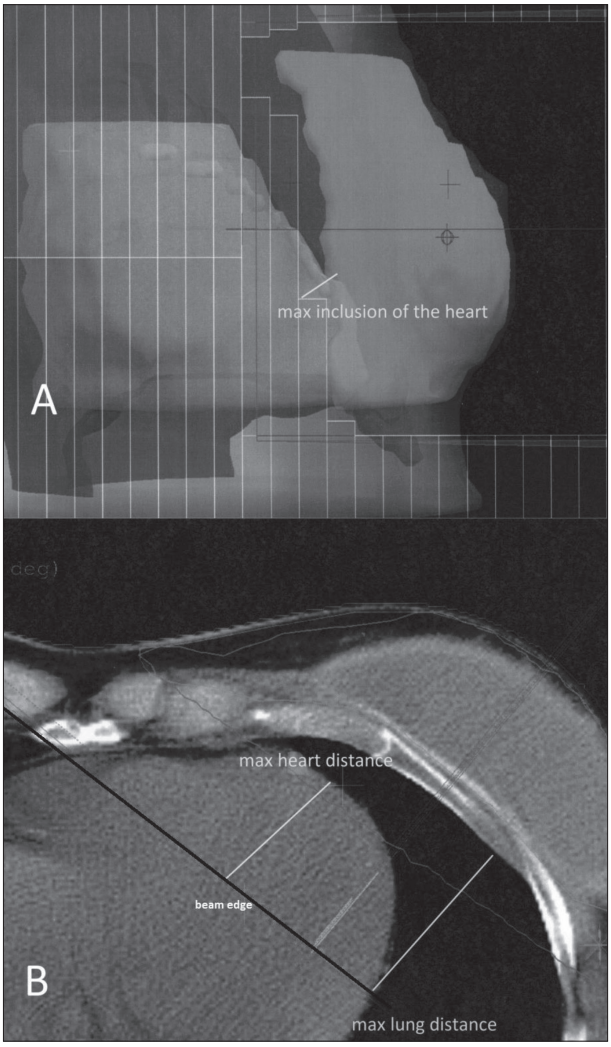


Figure 1. Beam's eye view of the heart (A) and measurements of maximum heart and lung distance (B)

(fluorouracil, doxorubicin, cyclophosphamide; adriamycin and cyclophosphamide; cyclophosphamide, methotrexate, fluorouracil, tamoxifen, docetaxel, paclitaxel, bevacizumab, trastuzumab, goserelin) have some degree of proven cardiotoxic effect [4, 12]. It has been confirmed in literature that tamoxifen cannot be associated with an increased incidence of heart diseases [13] but is correlated to an increased incidence of venous thrombosis and stroke [14].

Radiotherapy treatment

Prescribed doses to the breast were 60 Gy (66.6%) and 50 Gy (33.4%). The prescription to the supraclavicular region was 50 Gy (36%), while 20.2% of patients received an additional boost to the breast (10–12 Gy).

There were 58% patients who were treated to the breast only, 15% breast with boost, 25% breast with supraclavicular field and 2% breast, boost and supraclavicular field.

Calculated doses to heart and LAD and volumes are given in Table 1. The mean doses to the heart volume ranged among patients between 0.3 Gy and 62.4 Gy, with average of MHD of 4.6 Gy. The mean volume of the heart was 727 cm^3. As for the left lung, the maximum dose was 65.5 Gy (mean maximum 59.6 Gy), and average mean dose in the group 6.8 Gy. LAD, which was newly delineated, after the de-archiving of the treatment plans, received maximum of 62.1 Gy while the mean dose was 21.6 Gy. The mean volume of delineated LAD was 5.2 cm^3. The trend of maximum doses to LAD and heart, as well as lungs follow the increase of mean doses: higher the mean dose – higher the maximum dose.

Maximum heart distance (distance from radiation field edge to heart edge) and maximum lung distance (distance from radiation field edge to chest wall) were measured. The heart entered the irradiated volume by a mean length of 3.5 cm (but was shielded by multileaf collimator), while the left lung was included with a mean of 3.7 cm (also shielded by multileaf collimator). The heart was exposed to open beam by a mean value 1.4 cm. Measurements were done from the beam edge and presented in the Figure 1.

Cardiovascular evaluation

In total, 31 patients responded to the appointment with cardiologist. Out of this number, only four women never had any kind of heart associated diseases, while in other 27 women CVDs found were ranging from simpler hypertension to very complicated myocardial infarction (in total three patients). Out of the 31 evaluable patients, six patients had had a history of CVD before the treatment of breast cancer. Additionally, eight patients (26%) developed some form of cardiovascular disease during the first five years after treatment (phlebothrombosis, cardiomyopathy and myocardial infarction).

The data of all examined patients after cancer treatment are presented in Table 2.

Table 2. Cardiovascular diseases (CVD) in examined patients and complications developed eight years after treatment

Cardiovascular diseases (31 patients)	No. of patients with CVD*
Hypertension	14
Angina pectoris	3
Mitral valve insufficiency	2
Aortic valve stenosis	1
Tricuspid valve insufficiency	2
Venous disease	2
Hypertrophic cardiomyopathy	6
Chest pain (Stenocardia)	3
Phlebothrombosis	3
Myocardial infarction	3

*Some patients had more than one complication

The MHD of examined patients and their MLAD dose were correlated on Figure 2. The positive strong correlation ($r = 0.7772$, $p < 0.00001$) between MHD and MLAD dose was found.

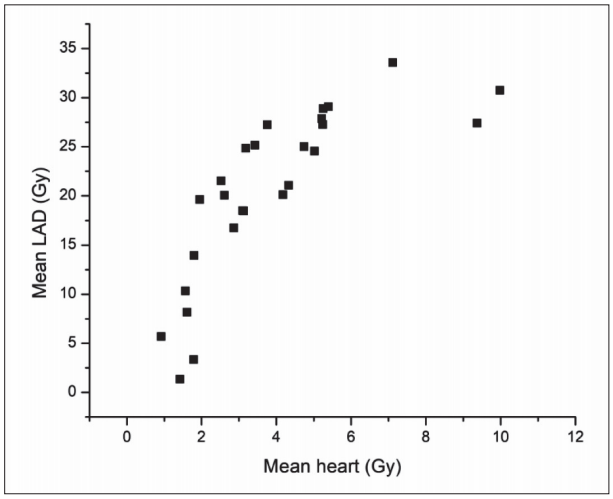


Figure 2. Correlation of mean heart dose to mean left anterior descending artery (LAD) dose for examined patients

Cardiovascular complications found in analyzed group were as follows: myocardial dysfunction and heart failure, coronary artery disease, valvular disease, arrhythmias, arterial hypertension, thromboembolic disease, peripheral vascular disease and stroke, pulmonary hypertension and pericardial complications.

Patients were graded according to the cardiotoxicity grading system given in literature-measured ejection fraction and other findings [14].

According to severity of CVD we divided all patients in four groups: Group 1 – venous disease and/or hypertension, group 2 – group 1 + arrythmia or coronary disease (angina pectoris), group 3 – group 2 + hypertrophy and/or cardiomyopathy, group 4 – group 3 + stenocardia/myocardial infarction. In the next step, we defined threshold values for MHD and MLAD for each group. Analyzing given data, we concluded that the results show a scoring system. Finally, after correlation od CVD group and mean doses values, our results have showed that patients can be divided in four scores (1–4) which is presented in Table 3.

Table 3. Scoring system developed based on complications and dose received by critical organs

Score	CVD complication groups	Mean heart dose (Gy)	MLAD artery dose (Gy)
1	Group 1: venous disease and/or hypertension	$x < 2$	$y < 10$
2	Group 2: Group 1 plus arrythmia or coronary disease (angina pectoris)	$2 < x < 3$	$10 < y < 20$
3	Group 3: Group 2 plus hypertrophy and/or cardiomyopathy	$3 < x < 5$	$20 < y < 25$
4	Group 4: Group 3 plus stenocardia/myocardial infarction	$x > 5$	$y > 25$

MLAD – mean LAD; LAD – left anterior descending artery; x – mean heart dose (Gy); y – MLAD artery dose (Gy); CVD – cardiovascular diseases

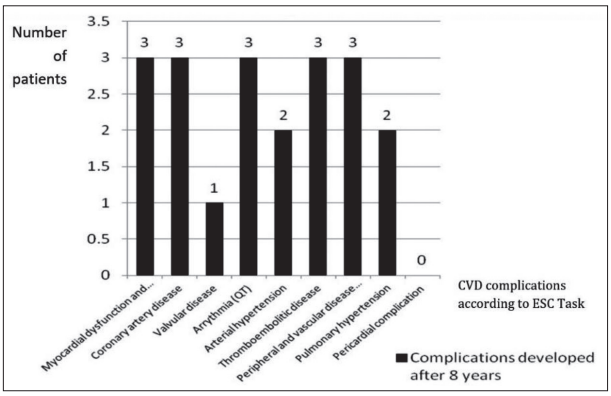


Figure 3. Cardiology complications developed in the examined group of 31 patient

Score 1 were patients with MHD < 2 Gy and MLAD < 10 Gy; score 2 – patients with MHD < 3 Gy and MLAD < 20 Gy; score 3 – patients with MHD < 5 Gy and MLAD < 25 Gy; score 4 – patients with MHD > 5 Gy and MLAD > 25 Gy. Our results showed that patients with MHD < 2 Gy and MLAD < 10 Gy had venous disease and/or hypertension; patients with MHD < 3 Gy and MLAD < 20 Gy developed venous disease and/or hypertension plus arrhythmia or coronary disease (angina pectoris); patients with MHD < 5 Gy and MLAD < 25 Gy developed venous disease, hypertension, arrhythmia, coronary disease (angina pectoris) and hypertrophy and/or cardiomyopathy; and patients with MHD > 5 Gy and MLAD > 25 Gy developed all previous diseases plus stenocardia and/or myocardial infarction, as shown in Table 3. The scoring system developed in this work is based on possible complication severity correlated to doses received by critical organs in our data, ranging from 1 to 4, and correlates with the values of doses to heart and LAD found in literature [11].

The positive correlations between mean doses to heart and CVD developed ($r = 0.9803$, $p < 0.003$), as well as

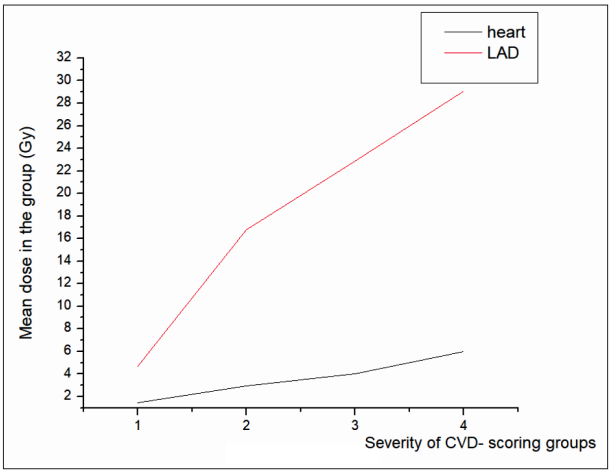


Figure 4. Correlation of the mean heart dose, mean left anterior descending artery (LAD) dose in the group and cardiovascular (CVD) complication scoring system

MLAD and clinical CVD developed ($r = 0.9803$, $p < 0.003$), significant at $p < 0.05$, was found on Figure 4.

At the time of treatment planning of these patients, only QUANTEC (Seoul, South Korea) parameters were available for treatment plan evaluation. According to QUANTEC, heart and its pericardium should be irradiated within following limits: mean dose < 26 Gy (our results in cardiologically examined group was 4.6 Gy), V30 Gy < 46% (our result 3.4%), and V25 Gy < 10% (our result 4%). LAD dose is not mentioned in QUANTEC. Lung V20 Gy according to QUANTEC should be < 30% (our result 10.4%) and mean dose with least complication probability 7 Gy (our result 6.8 Gy). Generally speaking, the average treatment planning dosimetry results in treatment plans were far below the indicated upper limits for long term cardiac or pulmonary complication probability, but contrary to the stated QUANTEC parameters, some form of CVD complications developed in majority of patients.

DISCUSSION

Breast cancer as the most common cancer in women worldwide, is curable in early stages thus survival can be long term. Since radiation therapy is an effective tool in the treatment of breast cancer, where structures in the heart, such as the LAD, are exposed to radiation, sparing the heart and its structures becomes significant issue in breast treatment planning.

It is evident from literature that the risk of major cardiovascular events becomes more pronounced five years after radiation therapy and continues to increase even for three more decades [15, 16]. Other studies reported cardiac events 10 years after initial radiotherapy treatment. The worst-case scenario is when irradiation worsens an already present CVD, or accelerates its appearance in cases where risk factors are present. Our results are in line with these findings: out of 31 examined patients, three had myocardial infarction and all of them had previous CVD before radiotherapy.

Between treatment and cardiology assessment, three patients had died, others could not be reached or could not show up for the appointment, while only 1/3 of recalculated and 1/4 of the total number of left breast patients treated in 2009, actually responded to cardiology evaluation.

There is evidence of strong correlation of dose distribution to the heart with the later developing cardiac effects which defines the increasing risk of major cardiac effect by MHD increase by 7.4% per 1 Gy of MHD [16]. The main strength of this paper is that it clearly correlates the doses received by the heart and LAD, to the cardiovascular complications developed after treatment. The cardiological assessment data of cancer survivors are now used as reference, for treatment plan strategy and evaluation. The results presented in our study correlate with published data [11, 17].

The most frequent cardiac problem reported during radiotherapy in the literature is acute pericarditis, pericardial effusion and arrhythmia [14]. In our investigation, none of our patients have reported cardiac problems during their treatment (according to hospital database reports). However, from the database of our cardiovascular clinic, there were two patients who requested clinical appointment immediately after radiation therapy and eight patients in the following five years.

During radiotherapy treatment planning and delivery, special attention should be paid to the use of cardiac shielding opportunities and modern techniques, such that the dose volume histogram reflects the need for sparing the heart and heart structures [18]. The implementation of deep inspiration breath hold (free or assisted) is the easiest way to naturally shield the heart by increasing the volume of air between the heart and chest wall where the tangential field edge is positioned [19, 20, 21], by the use of arc techniques – volumetric modulated arc therapy (VMAT) or advanced robotic accelerators [22, 23]. The optimal option for a significant decrease of dose to both lungs and heart is prone positioning but also use of immobilizing devices dedicated for both prone and supine breast radiotherapy [23, 24]. Assisted voluntary breath hold (ABC, Elekta), VMAT and both prone and supine breast irradiation are now available forms of treatment at our clinic.

Although all dosimetry parameters from the dose-volume histogram of treatment plans of examined patients were far below any clinically known limitation, it is clear that patient's heart and LAD may be severely damaged by radiation, especially if previous cardiovascular disease was registered [24]. Our results also confirm these findings. Severity degree of cardiovascular disease can be predicted according to the MHD and MLAD artery dose together, as we did in this work through the scoring system generated, but more detailed constraints are needed [25, 26]. Patients treated with radiotherapy for left-sided breast cancer, should remain in cardiology follow-up to diagnose possible cardiotoxicity [27].

The limitation of the current study is limited number of patients. Out of 114 initially selected patients, only 31 entered the final analysis. Definitive conclusions should be made after conducting prospective well-designed trial with more patients included.

The management of cardio-oncological patients requires a multidisciplinary approach to provide optimal care for patients. In that respect, these specialties will soon have to bring about new joint protocols, on management of cardio-oncological patients [28]. Propositions on management of cardiac toxicity are still under development and additional studies and research are needed, but it is recognized that a model predicting cardiology complication due to therapy is needed [29, 30]. The scoring system we proposed here serves in our institution as a predictor of CVD complications.

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Радиотерапија леве дојке – утицај доза на срце и леву предњу десцедентну артерију и развој кардиоваскуларне болести осам година после третмана

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САЖЕТАК

Увод/Циљ Болеснице оболеле од карцинома леве дојке, лечене радиолошком терапијом, у већем су ризику од настанка кардиоваскуларних болести (КВБ), с обзиром на то да је анатомским положајем део срца често у непосредној близини третиране регије, што у годинама после третмана може да изазове појаву кардиоваскуларних болести.

Циљ овог рада био је развој систем скоровања који идентификује болеснице са повећаним ризиком од развоја кардиоваскуларних болести, као последицу зрачења леве дојке.

Методе Болеснице које су праћене током ове студије зрачене су током 2009. године. Осам година касније позване су да учествују у студији током које су прегледане од стране кардиолога. Њихов налаз корелиран је са дозама које су током радиолошке терапије примили срце и лева предња десцедентна коронарна артерија (ЛАД).

Резултати Од 114 позваних болесница којима је током 2009. године зрачена лева дојка, 31 болесница се одазвала позиву на кардиолошки преглед. Од овог броја, шест болесница је имало кардиоваскуларну болест пре лечења малигне болести. Четири жене нису никад развиле ниједну кардиоваскуларну болест до кардиолошког прегледа, док су осталих 27 болесница развиле бар једну од КВБ, од хипертензије до инфаркта миокарда. Тежина кардиоваскуларне болести је у снажној позитивној корелацији са средњом дозом на срце и средњом дозом на ЛАД ($p = 0,003$).

Закључак Доза на критичне органе зависи од анатомије болесника, али и од радиотерапијске технике која је спроведена. Кардиоваскуларне компликације су доказана последица зрачења леве дојке. Тежина компликација зависи од односа између доза на срце и ЛАД изражена кроз систем скоровања. Систем скоровања заснован на дозама које примају срце и ЛАД поуздан је у предикцији развоја КВБ.

Кључне речи: кардиотоксичност; компјутерско планирање радиотерапије; карцином леве дојке; радиотерапија