Analysis of cardiac and pulmonary complication probabilities after radiation therapy for patients with early-stage breast cancer

Olga Utehina[1, 2], Sergejs Popovs[1, 2], Dace Purina[1, 2], Ingrida Slosberga[1, 2], Ilga Vevere[1, 2], Dzintars Emzins[1, 2], Juris Berzins[1, 2], Konstantinas Povilas Valuckas[3], Ernestas Janulionis[3], Albert Miller[3]

[1]Latvian Oncology Center, Riga Eastern Clinical University Hospital, [2]University of Latvia, Latvia, [3]Institute of Oncology, Vilnius University, Lithuania

Key words: *respiratory-gated radiotherapy; early-stage breast cancer; breast-conserving therapy; normal tissue complication probability.*

Summary. *Objective. The purpose of this study was to evaluate the radiobiological implications of clinical use of respiratory-gated techniques for postoperative radiation therapy of early-stage left-sided breast cancer after breast-conserving surgery.*

Material and methods. Radiation therapy treatment plans of 80 patients with early-stage breast cancer (stage I–II), receiving whole breast irradiation after breast-conserving therapy, were analyzed. The control group consisting of 47 patients received standard radiation therapy, and the respiratory-gated group consisting of 33 patients received deep inspiration-gated radiation therapy. Normal tissue complication probabilities (NTCP) for cardiac mortality and for clinical radiation-induced pneumonitis were calculated for all patients included in present study, using relative seriality model. NTCP data were analyzed for 113 radiation therapy plans, which included free breathing plans for the respiratory-gated groups.

Results. Pneumonitis probability was 0.6% (range 0.0–2.8%) and 0.3% (0.0–1.2%) for control and respiratory-gated group, respectively. Cardiac mortality was 1.3% (0.0–5.0%) and 0.2% (0.0–2.8%) for control and respiratory-gated group, respectively. Using respiratory-gated radiation therapy, NTCP was reduced in comparison with the control group by 83% ($P<0.00001$) and by 55% ($P=0.01270$) for cardiac mortality and for clinical radiation-induced pneumonitis, respectively.

Conclusions. Use of respiratory-gated radiation therapy, for postoperative treatment of early-stage breast cancer, significantly reduces excessive cardiac mortality probability and pulmonary complication probability, as compared to standard radiation therapy techniques. This is especially important from heart complication probability point of view, as cardiac mortality remains one of the important issues of postoperative breast irradiation in patients with early stage breast cancer.

Introduction

Radiotherapy is an essential part of breast-conserving therapy for patients with early stage breast cancer (1). Randomized trials conducted with a large number of patients have shown that radiotherapy (RT) after breast-conserving surgery significantly reduces local recurrence rate (2, 3). Furthermore, results of studies with more than 20-year follow-up have proven that lumpectomy with adjuvant whole breast RT for patients with early stage breast cancer equals to mastectomy by local recurrence rate and overall survival (2, 4).

Recent meta-analysis of data of trials performed worldwide has shown that RT after breast-conserving surgery significantly increases patient survival (5).

Study by Buchholz et al. demonstrated that for clinical stage II breast cancer, breast-conserving surgery with following RT provides statistically significant increase in survival, comparing to mastectomy without radiotherapy (6). Recently Vicini et al. demonstrated that some distant metastases could directly develop from recurrence in ipsilateral breast, so supporting the importance of local tumor control in the overall treatment of patients with breast cancer (7).

Standard RT method after breast-conserving surgery is whole remaining breast irradiation with two tangential fields (regional lymph nodes are irradiated according to indications) (8–10). During whole breast

Correspondence to O. Utehina, Latvian Oncology Center, Riga Eastern Clinical University Hospital, Hipokrata st. 4, 1079 Riga, Latvia. E-mail: olgautehina@mits.lv

irradiation, normal organs, such as lung and, in the case of left breast irradiation, heart, are unavoidably included in high-dose region, and so serious radiotherapy damage to these organs can occur (11–13). Early toxicity occurs mostly in skin tissue, but radiation dose does not induce heavy damage to skin, and such acute reactions are transient and clinically insignificant (10, 14). Late reactions, developing in healthy lung and heart tissue included in tangential fields, are clinically significant (14). Most significant heart RT complications are related to myocardium damage and are generally responsible for the excessive cardiac mortality in patients with breast cancer after radiotherapy (15–21). According to Gagliardi et al., excessive cardiac mortality in patients with breast cancer after whole breast irradiation with a prescribed dose of 50 Gy is 12% from myocardium damage and 9% from radiation damage of other heart structures (22). Multiple studies proved that probability of development of late complications in heart and lung (23–28) as well as grade of complications is correlated with relative organ volume, which receives clinically relevant dose (26, 29).

Clinical results of RT should be always balanced with probable acute and late radiotherapy complications (30–33). In order to reduce probability of the development of late complications, various modern RT technologies allowing sparing of normal tissues are introduced in clinical practice (10, 34).

According to data by Muren et al., significant heart and lung complication reduction is achieved using three-dimensional conformal radiotherapy (3D-CRT), comparing with two-dimensional conventional RT (11). However, even nowadays with wide use of 3D-CRT, excess cardiac mortality still persists in patients with breast cancer, receiving postoperative RT courses, as compared to normal age-matched female population (35).

In last few years, a new RT technique – respiratory-gated (RG) RT, using various patient breathing adaptation techniques – is being implemented in many clinics around the world. This method has potential to reduce significantly heart and lung RT complications, especially in case of postoperative whole breast irradiation (36). This is especially important in case of patients with early stage breast cancer, which nowadays have very good prognosis and long life expectancy (2, 4, 6).

It has been demonstrated in several studies that breathing adaptation techniques can be used to reduce the irradiated heart and lung volumes, primarily by utilizing lung inflation, which dilutes the amount of lung tissue in the radiation fields and separates the heart from the target, providing significant lung and heart dose reductions (37, 38). Two dose-modeling computed tomography studies have shown that both voluntary deep inspiration breath-hold and free breathing inspiration gating can provide similar lung and heart dose reductions (39, 40). Study by Pedersen et al. has shown that deep inspiration voluntary breath hold (DIVBH) respiratory-gated radiotherapy (RGRT) technique for breast cancer yields superior dosimetric consequences for all organs at risk as well as target volumes, comparing to free breathing and deep expiration breath hold irradiation techniques (39).

DIVBH RGRT technique is clinically implemented with the RPM system (Varian Medical Systems, Inc., Palo Alto, CA) at the Latvian Oncology Center. Pedersen et al. and Korreman et al. demonstrated that implemented DIVBH RGRT technique is reproducible and safe as well as maintains the target dose coverage and homogeneity and does not compromise doses to contralateral organs (39, 40).

The purpose of this study was to evaluate the radiobiological implications of clinical use of respiratory-gated techniques for postoperative radiotherapy of early-stage left-sided breast cancer. Normal tissue complication probability (NTCP) analysis for heart and lung has been performed to evaluate possible benefits of deep inspiration breath hold respiratory-gated radiotherapy in well selected group of patients. This is the first publication presenting results of application of RG radiotherapy to a homogeneous cohort of patients with early-stage breast cancer, as all studies published before included NTCP analysis for heterogeneous groups of patients, employing different target volumes and irradiation techniques.

Material and methods

Patient selection. Patients with left-sided breast cancer (stage I–II) were included in present study. All patients received breast-conserving surgery and hormonal and/or chemotherapy according to indications. Patients were randomized into two groups. First group received standard radiotherapy course, and second group – RG radiotherapy.

Starting from November 2006, RGRT was successfully performed for 33 women in Latvian Oncology Center of Riga Eastern Clinical University Hospital. Data of these patients were included in the present analysis as RGRT group. Forty-seven women were enrolled in the control group, which received standard three-dimensional conformal therapy treatment for whole breast. In total, data of treatment plans of 80 patients were analyzed in the current study.

Patient data acquisition and treatment planning. For RGRT group, the RPM system (Varian Medical Systems, Inc.) was used for respiration monitoring and manual prospective respiratory gating of a LightSpeed RT (GE Medical Systems) multi-slice scanner and gating of Clinac 2100 C/D (Varian Medical Systems, Inc.) medical linear accelerator. Before acquisition of computed tomography (CT) scan during preliminary training session, the patient was trained on DIVBH technique. DIVBH pattern was individualized to each patient, using manual audio breathing instructions. The patient was immobilized supine in indexed vacuum bag, with both arms above her head. The gating marker box was placed on the chest wall of the patient, on bony structure for breathing reproducibility, and outside radiation fields to avoid skin reactions. The CT scanning was performed as a manually prospectively gated spiral scan in the end-inspiration phase of respiration with a slice thickness of 3.75 mm. Free breathing (not gated) CT study was obtained prior to acquisition of the gated study. For control group, free breathing (not gated) CT study was performed using same positioning aids and scanning protocol. On each CT study of each patient, clinical target volume (CTV), including whole remaining breast and normal anatomy were contoured. CTV to planning target volume (PTV) expansion was performed in the same way for all patients in all groups, following usual clinical protocols. For RGRT group, contouring of target volumes and normal anatomy was performed as on gated as on not-gated CT studies. Conformal treatment plans, achieving full coverage of the remaining breast with 95% isodose, were individually optimized for each patient, with a prescription dose of 50 Gy (2 Gy/fraction, 5 weeks). Dose delivery was performed using 6 MV tangential photon fields with multileaf collimator (MLC) and wedges.

In both groups, equal boost dose (10 Gy in 5 fractions) was delivered by means of electron beam to lumpectomy cavity.

Cardiac and pulmonary complication probabilities were calculated for postoperative radiation therapy plans of 80 patients with early-stage left-sided breast cancer. Thirty-three patients received respiratory-gated radiation therapy (RGRT group) and 47 patients standard 3D-CRT (control group). Additional treatment plan on the free breathing CT series was created for each patient in the RGRT group. This allowed direct comparison of the clinical parameters of the free breathing (FB) and RG DIVBH treatment plans for each patient in the RGRT group.

In total, data of 113 treatment plans were analyzed in the present work: 33 deep inspiration gated radiotherapy plans and 80 FB plans.

Calculation of normal tissue complication probabilities. NTCPs for lung and heart were used for evaluation and comparison of treatment plans. NTCPs were calculated from dose volume histograms (DVH) of organs of interest using radiobiological modeling (10, 41, 42).

For each treatment plan, heart and lung NTCPs were calculated using relative seriality (RS) radiobiological model (43). Before calculation, DVH data were converted to the dose biologically effective to 2 Gy per fraction irradiation, using linear-quadratic model (α/β was equal to 3 Gy for both lung and heart) (44, 45). For the left lung, clinical pneumonitis of grade greater than 2 was used as endpoint in NTCP calculation. In the case of heart, NTCP calculation endpoint was excessive cardiac mortality in the irradiated patients with left-sided breast cancer. RS model coefficients used for lung and heart NTCP calculation in this study were obtained from data analysis of patients with breast cancer by Gagliardi et al. (22, 46).

Statistical analysis. NTCP data of control group were compared with RGRT group NTCP data, using Mann-Whitney *U* test. For the RGRT group, NTCP data of two treatment plans – deep inspiration and free breathing treatment plan – were compared for each patient using Wilcoxon test.

Results

Table 1 shows NTCP data for heart and left lung, calculated using RS model for all patients under investigation. The use of respiratory-gated radiotherapy leads to statistically significant reduction of the NTCPs for both heart and left lung. The mean NTCP values as well as interval of NTCP values are reduced for RGRT group.

Figure 1 shows excessive cardiac mortality probability steam and leaf plot for the respiratory-gated and standard radiation therapy groups. Plot for the control group shows a wider extension of quartiles as compared to the RGRT group. Plot for the RGRT group shows compact probability distribution and lower mean NTCP value in comparison with plot for the control group. Central quartiles of NTCP values do not cross between two plots.

Figure 2 shows radiation-induced pneumonitis probability steam and leaf plot for the respiratory-gated and standard radiation therapy groups. Plot of NTCP values for the RGRT group shows lower mean NTCP value and more compact probability distribution as

Table 1. **Heart and left lung normal tissue complication probabilities data**

Parameter	Standard radiation therapy		Respiratory-gated radiation therapy		Parameter relative reduction (%)	*P*
	mean (%)	interval (%)	mean (%)	interval (%)		
Probability of excessive cardiac mortality	1.3	0.0–5.0	0.2	0.0–2.8	83	<0.00001
Probability of clinical pneumonitis	0.6	0.0–2.8	0.3	0.0–1.2	55	0.01270

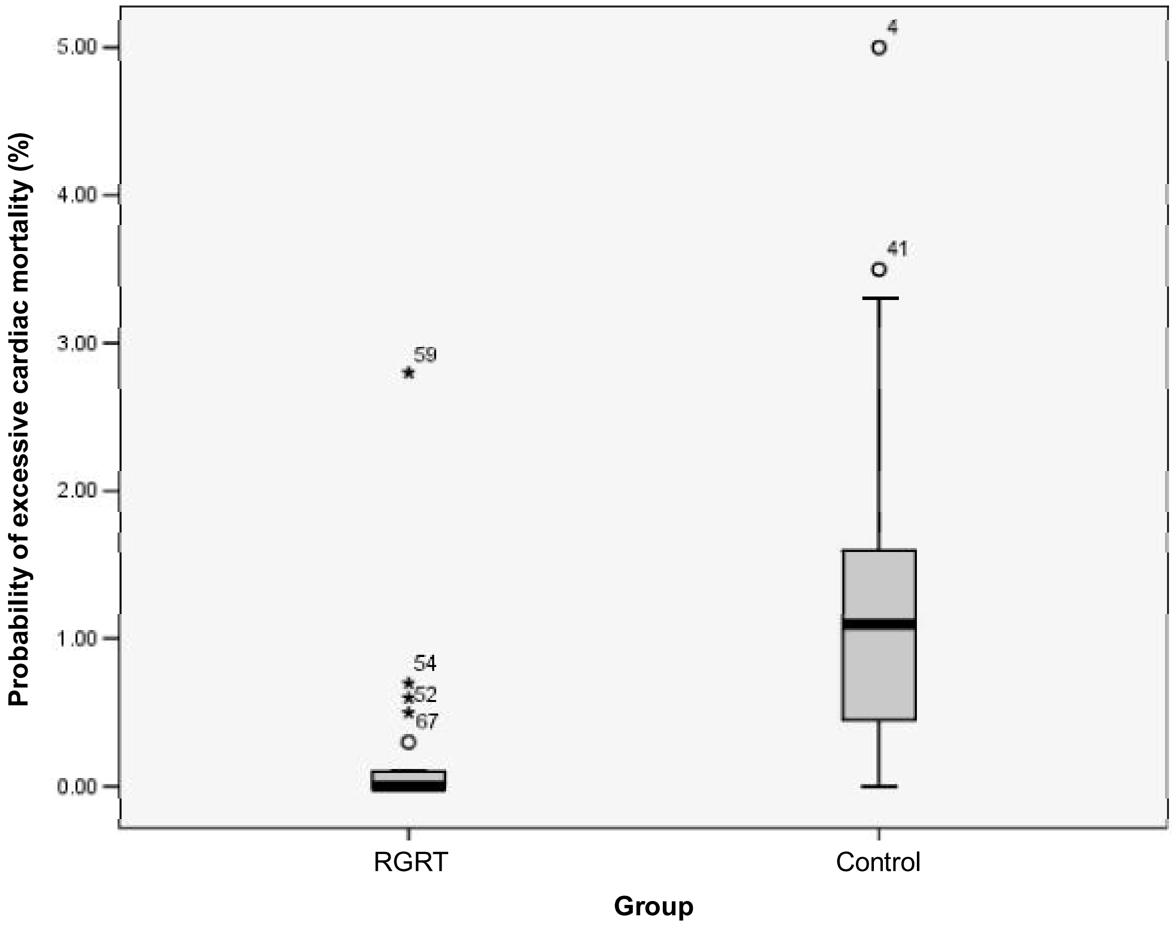

Fig. 1. **Excessive cardiac mortality probability steam and leaf plot for the respiratory-gated and standard radiation therapy groups**

compared to NTCP values plot of the control group.

Table 2 shows the compilation of NTCP data for group, which received respiratory-gated radiation therapy, presenting results of analysis of NTCP data for two treatment plans for each patient in the RGRT group – treatment during deep inspiration breath cycle breathing cycle phase (DIVBH plan) and treatment during free breathing (FB plan). Application of respiratory-gated radiotherapy leads to statistically significant reduction of the NTCP for both heart and left lung. The mean NTCP values as well as interval of NTCP values are significantly reduced for the RGRT group.

Figure 3 shows excessive cardiac mortality probability steam and leaf plot for radiation therapy gated at deep inspiration and free breathing radiation therapy treatment plans of patients in the RGRT group. Data of FB plans show wider extension of quartiles as compared to DIVBH plans. Plot for DIVBH plans shows a compact probability distribution and lower mean

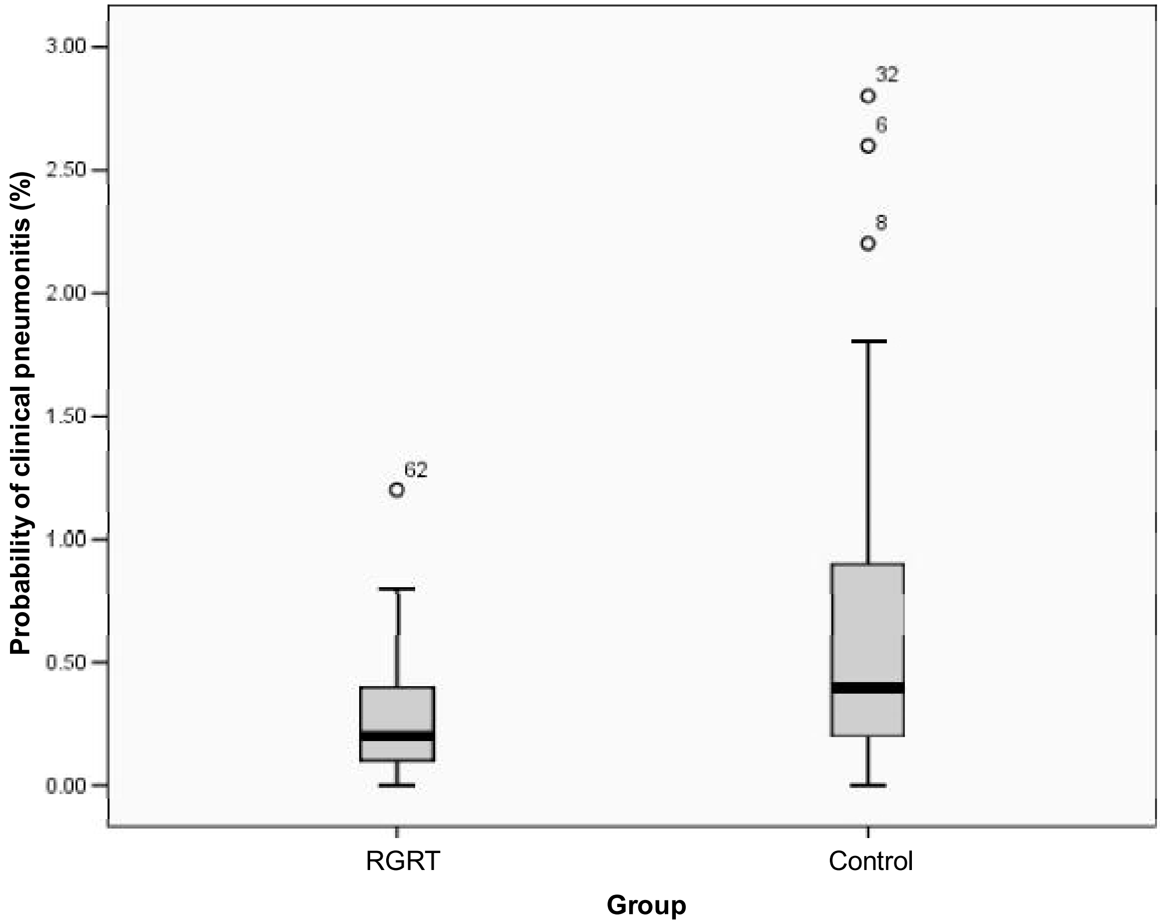

Fig. 2. **Radiation induced pneumonitis probability steam and leaf plot for the respiratory-gated and standard radiation therapy groups**

Table 2. **Heart and left lung normal tissue complication probabilities data for radiation therapy gated at deep inspiration and free breathing radiation therapy**

Parameter	Free breathing		Deep inspiration breath hold		Parameter relative reduction (%)	*P*
	mean (%)	interval (%)	mean (%)	interval (%)		
Probability of excessive cardiac mortality	1.5	0.0–9.0	0.2	0.0–2.8	86	0.00008
Probability of clinical pneumonitis	1.0	0.1–3.6	0.3	0.0–1.2	71	0.00012

NTCP value in comparison with plot for FB plans. Central quartiles of NTCP values do not cross between two plots.

Figure 4 shows radiation-induced pneumonitis probability steam and leaf plot for radiation therapy gated at deep inspiration and free breathing radiation therapy treatment plans of patients in the RGRT group. Plot of NTCP values of DIVBH plans shows lower mean NTCP value and more compact probability distribution as compared to plot of NTCP values of FB plans.

Discussion

In last years, the number of patients with early-stage breast cancer is increasing worldwide (47). Breast-conserving therapy with surgery and postoperative radiotherapy is used more frequently (8, 48). Patients with early-stage breast cancer have an excellent prognosis and long life expectance, so it is very important to reduce manifestation rate of serious late complications to absolute minimum (49). Late complications negatively affect life quality and can lead to patient death (13, 16–19).

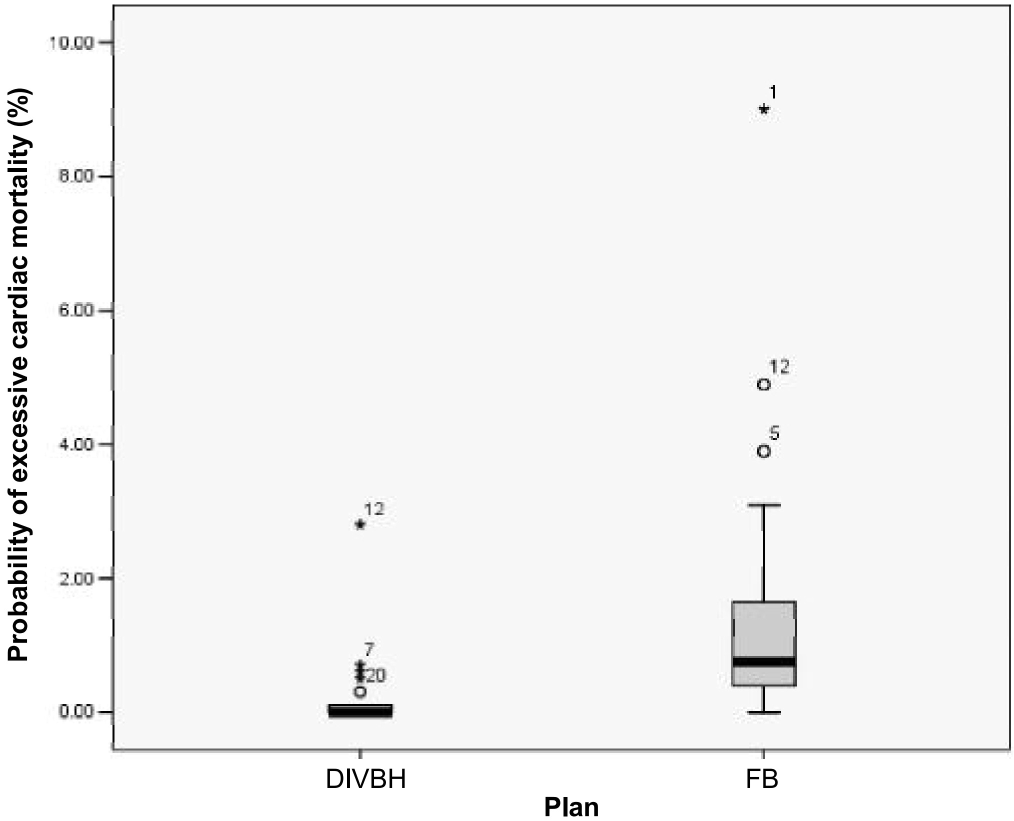

Fig. 3. **Excessive cardiac mortality probability steam and leaf plot for radiation therapy gated at deep inspiration and free breathing radiation therapy treatment plans in the respiration-gated radiotherapy group**

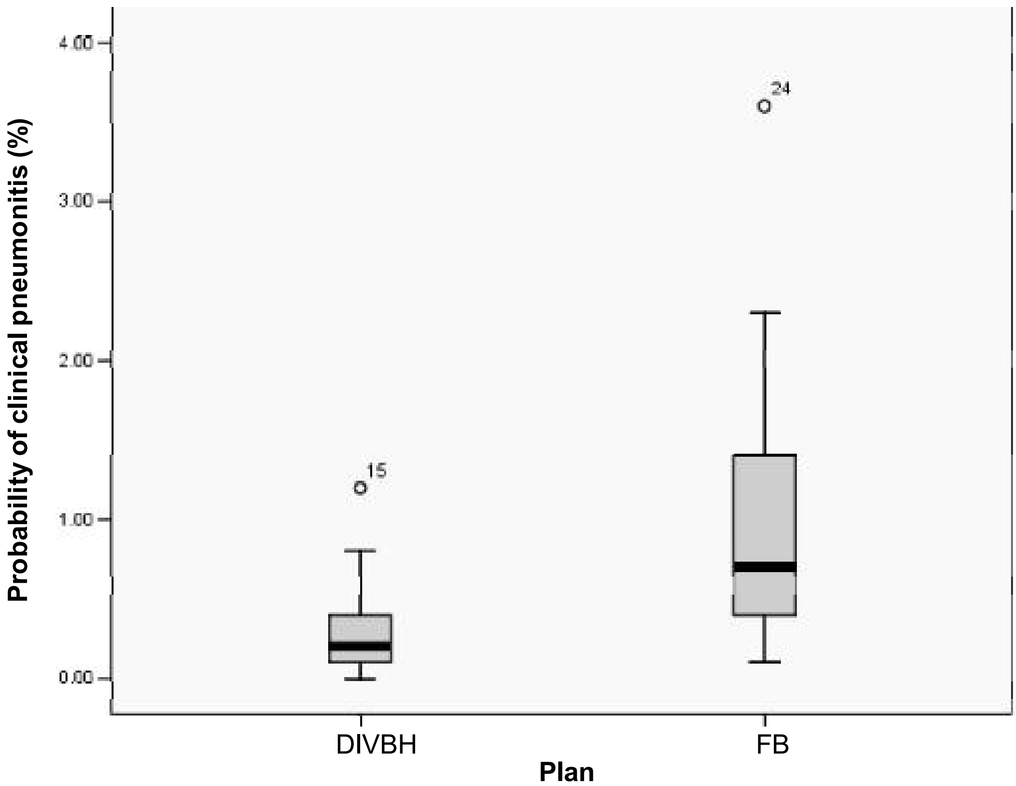

Fig. 4. **Radiation induced pneumonitis probability steam and leaf plot for radiation therapy gated at deep inspiration and free breathing radiation therapy treatment plans in the respiration-gated radiotherapy group**

The aim of radiotherapy is not only to cure patient from cancer, but also to achieve high quality of life after completion of radiotherapy. That is why it is essential to introduce new normal tissue sparing radiotherapy methods into clinical practice, to achieve better balance between necessarily aggressive treatment and radiotherapy complications.

NTCP analysis even nowadays cannot be used directly for radiotherapy plan evaluation, but it is a very important tool for comparison of radiotherapy plans and even different radiotherapy methods (10). NTCP analysis can assist in finding of new ways to reduce radiotherapy-induced complication rate (22, 46).

Respiratory-gated (breathing adapted) radiotherapy is a new radiotherapy method, recently introduced into clinical practice. In 2006, Korreman et al. published the first review on clinical data devoted to heart and lung NTCP reduction, using breathing adapted radiotherapy in patients with breast cancer (50). Patients, which received radiotherapy to breast and regional lymph node areas, comparing deep inspiration breath hold technique with free breathing technique and free breathing, deep inspiration-gated technique were included in that investigation. Main conclusion of Korreman et al. was that radiotherapy with synchronization on deep inspiration significantly reduces heart and lung NTCP for patients with breast cancer.

In our investigation, data of the patients with early-stage breast cancer, which underwent breast-conserving surgery and received postoperative radiation therapy only to left breast, are analyzed. At present moment, this is the only published study, which includes respiratory-gated radiotherapy plan analysis for such a homogeneous group of breast-conserving therapy patients (37, 50, 51).

In the group, receiving standard radiation therapy, mean heart complication probability was 1.3%, but in the RGRT group, the mean value of this parameter was 0.2%. Mean lung complication probability was 0.6% and 0.3% for groups, which received standard radiotherapy and RGRT, respectively.

Using RGRT, excessive cardiac mortality probability was reduced by 83% as compared to the control group (P<0.00001). Reduction of this parameter allows concluding that live expectancy of these women will not be reduced due to radiation therapy complications. This is a very important result of present study, proving clinical benefit of RGRT in case of breast-conserving therapy for patients with early-stage left-sided cancer.

Pneumonitis probability was reduced in the RGRT group by 55%, in comparison with the standard radiation therapy group (P=0.01270).

NTCP data analysis of two plans for each patient in the RGRT group (deep inspiration plan and free breathing plan) has shown a statistically significant reduction of heart and lung complication probabilities, achieved by the use of deep inspiration-gated radiation therapy. Using treatment gated on deep inspiration, the mean value of excessive cardiac mortality probability was reduced by 86% as compared with free breathing radiotherapy plans of the same patients (P=0.00008). Maximal value of excessive cardiac mortality probability in free breathing plans was 9.0%, which was reduced to 0.6% by the use of DIVBH respiratory-gated radiation therapy. The mean value of lung pneumonitis probability was reduced by the use of RGRT by 71% (P=0.00012).

Remouchamps et al. and Koremann et al. recently performed two NTCP evaluation studies on respiratory-gated radiotherapy (37, 50). Study by Remouchamps et al. has shown a significant reduction of heart and lung complication probabilities using moderate DIBH with active breathing control device as compared with FB radiotherapy (37). Using moderate DIBH, the mean lung NTCP was reduced by 66% and mean heart NTCP was reduced by 85% (37). Study by Koremann et al. has shown the results comparable to study by Remouchamps et al.: the mean NTCPs were reduced by 81% and 94% for lung and heart, respectively (50). In both mentioned studies, NTCP values for excessive cardiac mortality were calculated using the same RS model and the same coefficients as in the present study. For lung tissue, both Remouchamps et al. and Koremann et al. were using different radiobiological model (37, 50), with coefficients obtained by Kwa et al. from a heterogeneous set of data, including lung cancer and Hodgkin disease irradiation (26). Furthermore, abovementioned studies by Koremann et al. and Remouchamps et al. included data of a heterogeneous set of patients, with some of the patients receiving radiation therapy with deep tangential fields, for inclusion of internal mammary nodes in volume of therapeutic dose (37, 50). This can explain greater advantage in heart and lung sparing as compared to results of the present study.

A statistically significant NTCP reduction achieved by the use of respiratory-gated radiotherapy for patients with early-stage breast cancer is a very important result of the present study. Expected lifespan of these patients is long, and goal of the treatment is not only to treat cancer, but also not to induce serious injury in these otherwise healthy patients. Reduction of cardiac and pulmonary complications allows insuring high quality of life of treated patients with early-stage breast cancer.

Conclusions

Use of respiratory-gated radiation therapy, gated on deep inspiration, for postoperative treatment of patients with early-stage breast cancer significantly reduces excessive cardiac mortality probability and serious pulmonary complication probability, as compared with standard radiation therapy techniques. Mean probability of excessive cardiac mortality was reduced by use of respiratory-gated radiotherapy by 82% as compared with the control group and by 75% as compared with free breathing plan of the same patient. Mean probability of lung pneumonitis was reduced by use of respiratory-gated therapy by 53% as compared with the control group, and by 59% as compared with free breathing plan of the same patient. This is especially important from point of view of heart complication probability, as excessive cardiac mortality remains one of the important issues of postoperative breast irradiation in patients with early-stage breast cancer.

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Sergančiųjų krūties vėžio ankstyvosiomis stadijomis širdies ir plaučių komplikacijų tikimybių analizė po spindulinio gydymo

Olga Utehina[1, 2], Sergejs Popovs[1, 2], Dace Purina[1, 2], Ingrida Slosberga[1, 2], Ilga Vevere[1, 2], Dzintars Emzins[1, 2], Juris Berzins[1, 2], Konstantinas Povilas Valuckas[3], Ernestas Janulionis[3], Albert Miller[3]

[1]Rygos Rytų klinikinės universitetinės ligoninės Latvijos onkologijos centras,
[2]Latvijos universitetas, Latvija, [3]Vilniaus universiteto Onkologijos institutas, Lietuva

Raktažodžiai: spindulinis gydymas su kvėpavimo kontrole, ankstyvųjų stadijų krūties vėžys, krūtį tausojamasis gydymas, normalių audinių komplikacijų tikimybė.

Santrauka. *Tikslas.* Šios studijos tikslas – įvertinti radiobiologinę postoperacinio spindulinio gydymo su kvėpavimo kontrole klinikinę reikšmę sergančioms ankstyvąja kairės krūties vėžio stadija po krūtį tausojamosios operacijos.

Duomenys ir metodai. Išanalizuota 80 sergančiųjų ankstyvosios stadijos krūties vėžiu (I ir II stadijų) spindulinis gydymas, kai buvo švitinama visa krūtis po tausojamosios operacijos. Kontrolinę grupę sudarė 47 ligonės, kurioms buvo skirtas standartinis spindulinis gydymas, ir grupę su kvėpavimo kontrole (RG) sudarė 33 ligonės, kurioms buvo skirtas spindulinis gydymas su kvėpavimo kontrole giliai įkvepiant. Normalių audinių komplikacijų tikimybė, sukelianti širdies komplikacijas ir kliniškai patvirtintą spindulinį pneumonitą, apskaičiuota visoms šios studijos pacientėms naudojant santykinio nuoseklumo (angl. *relative seriality*) modelį. Išanalizuota 113 spindulinio gydymo planų, įskaitant ir laisvo kvėpavimo planus grupėje su kvėpavimo kontrole.

Rezultatai. Pneumonito tikimybė buvo 0,6 proc. (intervalas 0,0–2,8 proc.) ir 0,3 proc. (0,0–1,2 proc.), atitinkamai kontrolinėje grupėje ir grupėje su kvėpavimo kontrole. Širdies komplikacijų atsirado 1,3 proc. (0,0–5,0 proc.) ir 0,2 proc. (0,0–2,8 proc.), atitinkamai kontrolinėje grupėje ir grupėje su kvėpavimo kontrole. Taikant spindulinį gydymą su kvėpavimo kontrole, normalių audinių komplikacijų tikimybė buvo sumažinta 83 proc. ($p<0,00001$) ir 55 proc. ($p=0,01270$), atitinkamai širdies komplikacijoms ir kliniškai patvirtintam pneumonitui.

Išvados. Spindulinis gydymas su kvėpavimo kontrole, skiriamas ankstyvosios stadijos krūties vėžiui gydyti, žymiai sumažina papildomų širdies komplikacijų ir plaučių komplikacijų tikimybę palyginus su standartiniais spindulinio gydymo metodais. Tai ypač svarbu dėl širdies komplikacijų tikimybės, nes širdies komplikacijos yra viena svarbiausių ankstyvosios stadijos pooperacinio spindulinio krūties vėžio gydymo problemų.

Adresas susirašinėti: O. Utehina, Rygos Rytų klinikinės universitetinės ligoninės Latvijos onkologijos centras, Hipokrata 4, 1079 Ryga, Latvija El. paštas: olgautehina@mits.lv

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