Late cardiopulmonary complications
in breast cancer patients following combined adjuvant treatment

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Aim. The aim of the study was to evaluate late toxicity from heart and lungs in breast cancer patients treated with mastectomy and adjuvant sequential chemotherapy and radiotherapy (Chth and Rt).

Material and methods. Forty seven women (mean age 47 years) with stage T1-4N0-2 M0 breast cancer, treated with mastectomy and adjuvant sequential chemotherapy and radiotherapy were examined in order to assess the side-effects in the heart and the lungs. All patients underwent chemotherapy: 40 received chemotherapy including antracyclines, 7- without antracyclines. Radiotherapy was undertaken in all cases. It was administered after chemotherapy and was planned according to the well-established technique. It included the chest wall and regional lymph nodes with a specified dose of 46-50 Gy administered in daily fractions of 2Gy. The high resolution computed tomography HRCT of the lungs was performed after a mean time of 17 (13-28) months and then, after a mean time of 33 (28-58) months. The condition of the heart was studied using electrocardiography (ECG) and echocardiography (ECHO), which were performed before combined treatment and then after a mean time of 17 and 33 months from its completion.

Results. Heart: 7 patients had an abnormal echocardiogram (ventricular dilatation, abnormal Left Ventricular Ejection Fraction, disordered left ventricular contractility, worsening of pre-existent valvular disease). All 7 had received chemotherapy including antracyclines. In 5 of them the echocardiographic defects were asymptomatic and reversible during the time of observation. In 2 patients moderate toxicity was observed. The analysis of isodose distribution excluded radiotherapy as a factor influencing toxicity, but seems to indicate a connection with antracyclines.

Lungs: The first examination (after a mean time of 17 months) revealed no changes in 24 patients. There were 19 fibrotic changes in lung apex and 19 cases of parietal fibrosis. In the second examination (after a mean time of 33 months), there were no changes in 24 patients and 22 fibrotic changes in lung apex and 13 cases of parietal fibrosis. All these changes were discrete, asymptomatic and the parietal fibrosis was invisible in the chest X-rays. The analysis of the evolution of fibrotic changes revealed that parietal fibrosis had a tendency to regression, but the apical ones are unpredictable: some of them do regress, but others – progress. The probability of parietal fibrosis did not depended on type of chemotherapy (p=0.64), but significantly depended on the depth of 50% isodose in the lung (p<0.05).

Conclusions. Postoperative radiotherapy as an element of combined adjuvant treatment in breast cancer, administered in conventional fractionated doses, causes no clinically significant lesions in the lungs and heart. The analysis of the distribution of isodoses in the heart showed, that clinically important myocardial changes, observed in two patients, were not connected with radiotherapy. Probably, they were connected with epirubicin chemotherapy. Correctly planned postoperative radiotherapy is a safe therapeutic method causing no significant disturbances of the functions of vital organs during the mean follow-up period of 33 months.

Ocena późnych powikłań ze strony serca i płuc u chorych na raka piersi
po skojarzonym leczeniu uzupełniającym

Cel. Celem pracy była ocena późnej toksyczności ze strony serca i płuc u chorych na raka piersi po mastektomii oraz uzupełniającej chemioterapii i radioterapii.

Materiał i metoda. Badaniu poddano 47 kobiet (średnia wieku 47 lat) z rakiem piersi w stopniu zaawansowania T1-4 N0-2 M0. Po mastektomii, u wszystkich chorych przeprowadzono chemioterapię i radioterapię. U 40 zastosowano programy z antracyklinami, u 7 – bez antracyklin. Radioterapię przeprowadzono według tej samej techniki, po zakończeniu

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leczenia chemicznego. Napromieniono ścianę klatki piersiowej i okolice węzłowe (46-50 Gy / 2Gy). W celu oceny zmian w płucu, po stronie leczonej, zastosowano badanie tomograficzne komputerowe o wysokiej rozdzielczości HRCT, które przeprowadzono po średnim czasie 17 miesięcy (13-28) i 33 miesięcy (28-58) od zakończenia leczenia skojarzonego. W celu oceny serca zastosowano badanie EKG i echokardiograficzne, które przeprowadzono przed rozpoczęciem leczenia skojarzonego, a następnie po średnim czasie 17 i 33 miesięcy od jego zakończenia.

Wyniki. Serce: U 7 chorych (wszystkie leczone antracyklinami) stwierdzono nieprawidłowości w echokardiogramie (poszerzenie i zaburzenie kurczliwości lewej komory, obniżenie LVEF, nasilenie istniejących wad serca). U 5 z nich zmiany były bezobjawowe i odwracalne. U 2 chorych stwierdzono klinicznie jawną, miernie nasiloną niewydolność serca, która wydawała się mieć związek z podaną epirubicyną. Na podstawie analizy rozkładu izodoz wykluczono napromienianie jako przyczynę zmian w sercu.

Płuca: W badaniu po średnim czasie 17 miesięcy u 24 pacjentek obraz płuc był prawidłowy. U 19 stwierdzono zwłóknienia w szczycie płuca po stronie napromienianej, a u 19 zwłóknienia przyścienne. W kolejnym badaniu po średnim czasie 33 miesięcy u 24 chorych nie było zmian w płucach, u 22 stwierdzono zwłóknienia w szczycie i u 13 - zwłóknienia przyścienne. Zmiany były mało nasilone, bezobjawowe i niewidoczne w konwencjonalnym zdjęciu rentgenowskim klatki piersiowej. Zwłóknienia przyścienne miały tendencję do regresji w czasie. Zwłóknienia w szczycie płuca, u części chorych ulegały regresji, u innych – progresji. Prawdopodobieństwo pojawienia się zwłóknienia nie miało związku z typem chemioterapii (p=0,64), a zależało od głębokości izodozy 50% w płucu (p<0,05).

Wnioski. Radioterapia pooperacyjna, w dawkach konwencjonalnych, nie powodowała klinicznie znaczących zmian w płucu ani sercu. Klinicznie jawne nieprawidłowości ze strony serca, stwierdzone u 2 chorych, nie miały związku z radioterapią, lecz mogły mieć związek z epirubicyną. Dotychczasowa obserwacja chorych pozwala przypuszczać, że prawidłowo zaplanowana radioterapia pooperacyjna jest bezpieczną metodą leczenia.

Introduction

Present treatment of breast cancer is based on a combination of available methods. The principle of adjuvant therapy after mastectomy is presently the use of chemotherapy combined with radiotherapy. While the usefulness of chemotherapy has never been questioned, the role of postoperative radiotherapy has been subject to controversy over many years. However, three recent reports of controlled studies confirmed the beneficial effects of well performed postoperative radiotherapy. In the Danish study [1] of high risk for local or regional recurrence premenopausal women it was shown that radiotherapy reduced that risk from 32% to 9% (p=0.001) and increased 10-year survival from 45% to 54%. Similar results were obtained also in postmenopausal women in whom radiotherapy reduced that risk from 35% to 8% and increased 10-year survival from 36% to 45% (p=0.001) [2]. In the Canadian controlled study postoperative radiotherapy reduced the risk of local and regional recurrences from 25% to 13% and improved total 10-year survival from 56% to 65% [3].

However, combined treatment is associated with higher early and late toxicity. This is particularly true of radiotherapy combined with anthracyclines. Only scant data is available on late reactions to anthracyclines in doses used in adjuvant treatment, but it is known that they potentiate cardiac damage induced by radiotherapy [4].

Presently our objectives include not only possible cure, but also adequate quality of life of the patients and, in view of this, the proportion of late complications of this treatment has become an important problem in modern oncology. Our interest should be focused on late sequelae of combined treatment. This is particularly important in the case of combined treatment with radiotherapy and anthracyclines and/or taxoids.

Study aim

The aim of the study was to assess the late toxicity of combined postoperative treatment using chemotherapy and radiotherapy in patients with breast cancer. Late toxic effects were assessed in the heart and lungs.

Material and methods

The prospective study began in November 1996. The study group comprised 47 patients with breast cancer in stage T1-4, N0-2, M0. Their mean age was 47 years (range 31 – 68 years). In 26 patients the right breast and in 21 the left breast was involved. The indication to adjuvant treatment, pre- and /or postoperative, was tumour size T3, T4 or G3 and/or involvement of at least four lymph nodes in the axilla. Forty patients received chemotherapy with anthracacyclines according to the following programmes: 1) 4 courses of epirubicin and 4 courses of CMF (cyclophosphamide, methotrexat, 5-fluorouracil); 2) EC (epirubicin, cyclophosphamide); 3) AC (doxorubicin, cyclophosphamide); 4) CMF (cyclophosphamide, methotrexate, 5-fluorouracil). Seven patients received chemotherapy without anthracyclines: 6 courses of CMF. Radiotherapy was administered after chemotherapy, after a mean interval of 24 days. All patients received radiotherapy according to the technique proposed by the Maria Sklodowska-Curie Memorial Cancer Centre and Institute of Oncology in Warsaw. The modern system planning was used before treatment in all patients. After marking out the area of ir-

radiation on a simulator, computed tomography slices were performed to assess the target volume and topography of critical organs. The plans of treatment were made using three-dimmentional computed treatment planning system Helax. The dose-volume histograms in lung and heart were analysed before the start of irradiation. The depth of the isodose 50% in heart and lung was measured in 7 computed tomography slices, in every patient. The irradiated areas were: supraclavicular, posterior axillary, sternal and scar area. Fractions of radiation were conventional: 2 Gy / day. The beam and administered doses were typical: Co-60 or photons 4-6 MeV, 50 Gy in 25 fractions to the supraclavicular area; 50 Gy to the axillary area calculated in the depth of the axilla from the supraclavicular and posterior axillary fields; the sternal area and the scar area were irradiated with electrons of individually chosen energy (6-18MeV), in 46 Gy/80% dose. The mean time of radiotherapy was 51 days. Excluded from the study were patients who received incomplete doses, or were not given irradiation to all node areas, who received fraction dose over 2 Gy, who received irradiation to chest wall from two oblique fields, or who had not been given chemotherapy. After literature review [5] sequential treatment mode was chosen with radiotherapy beginning 2-4 weeks after completion of chemotherapy. The material is presented in Table I.

Table I. Material

No of cases	47
Age (years)	31-68 (mean 47)
Breast: right	26
left	21
Stage	T1N1M0-T4N2M0
II	26
III	21
Chemotherapy: with antracyclines	40
without antracyclines	7

H e a r t . The condition of the heart was studied using electrocardiography (ECG) and echocardiography (ECHO). The examinations were carried out before combined treatment and then after over one year and over two years from its completion. The first control examination was carried out after a mean time of 17 months (13-28 months), the second one after a mean time of 33 months (28-58 months). In the echocardiographic examination attention was paid to: pericardium, dimensions of atria, ventricles and aorta, appearance of valves, blood flow across the ostia, thickness of heart walls and septum, contractility of ventricles, end-diastolic and end-systolic pressure in left ventricle, left ventricular ejection fraction (LVEF), ventricular relaxation. The authors intended to answer the question, whether possible cardiac function disturbances were due only to chemotherapy, only to radiotherapy or the combination of these methods. On the basis of pertinent literature we assumed that segmental con-

tractility disorders and/or ischaemia of the anterior wall and septum were the results of toxic effects of radiotherapy. Chemotherapy could lead to contractility disturbances of the whole left ventricle and disordered valvular function [6]. Literature reports on disturbances in valves and in high ventricular volume after radiotherapy concerned exclusively patients with Hodgkin disease, and could not be used for comparison with breast cancer because of a different radiotherapy technique and high heart volume in irradiation area [7].

L u n g s . Late postradiation lesions of the lungs take the form of fibrosis, mostly on pulmonary apex after photon beam irradiation and on scar area, near the chest wall, after electron beam. For the evaluation of fibrosis grade and volume of fibrotic changes high resolution computed tomography (HRCT) was applied. The first examination was carried out after a mean time of 17 months (13-28 months) and the second one after a mean time of 33 months (28-58 months) after completion of chemotherapy and radiotherapy. The purpose of these examinations was an evaluation of the incidence and dynamics of fibrotic changes in the lungs and establishing whether radiation-induced pulmonary lesions lead to clinical symptoms and affect the physical condition of the patients. It was also attempted to assess whether the technique of electron beam treatment expressed as the depth of 50% isodose in pulmonary tissue could influence the development of late radiation-induced lesions. The degree of fibrotic lesions was assessed using the classification of the work of M. Overgaard [8], presented in Table II. The degree of fibrosis was established comparing the involved pulmonary area with the same area in healthy lung.

S t a t i s t i c a l   a n a l y s i s

To compare the percentage of fibrosis in irradiated lung after a mean time 17 and 33 months, the Mc Nemar test was used. To find out whether the lung fibrosis depended on type of chemotherapy (with or without antracyclines), the chi square (Yates' modification) test was used. To assess whether the percentage of lung fibrosis depends on the depth of isodose 50%, nonparametric test Kołomogarow-Smirnow was used.

Results

H e a r t

In 7 out of 47 patients echocardiographic changes were disclosed after a mean time of 17 months after completion of chemotherapy and radiotherapy. Six patients were treated according to the programme: 4 courses of epirubicin and 4 courses of CMF, one patient received 4 EC courses and 3 AC courses. Five patients received radiotherapy to the right breast and two to the left. In two patients the changes involved cardiac valves and were diagnosed already before treatment beginning (aortic

Table II. Classification of the intensity of late radiation-induced reactions in lung
(from M. Overgaard. *Radiat Oncol* 1987; 9:1-12)

Grade	Late reactions
0	No changes
1	Mild changes: slight, tiny, scattered fibrous densities in exposed area
2	Moderate changes: evident, more confluent fibrotic densities in exposed area with slight retraction of surrounding lung tissue
3	Severe changes: confluent, irregular densities in exposed area with definite retraction of surrounding lung tissue

regurgitation and mitral regurgitation), and during first year after chemotherapy and radiotherapy, reversible worsening on valvular condition was noted. In five patients impairment of left ventricular contractility was observed in the form of global hypokinesis or relaxation disturbances. In one of them, after 13 months, fresh aortic regurgitation was noted – clinically important but regressing after treatment with angiotensin convertase inhibitors (ACE) after 27 months. In five patients echocardiographic changes were clinically silent and were reversed during treatment with ACE inhibitors. In two patients moderately intense toxicity with cardiac failure, NYHA grade II, was observed after 18 months and 22 months, and the symptoms persisted during the second control examination without evidence of progression in later examination 31 and 34 months after treatment with perindopril. One of these patients had received radiotherapy to the left breast, the other one to the right breast. Both had been treated according to the programme: 4 epirubicin and 4 CMF courses. In both cases the total dose of epirubicin was 400 mg/m^2. In both patients dilatation of the left ventricle was found with global hypokinesis and LVEF decrease, while ECG showed ischaemia of anterior and lateral cardiac walls. In one patient with evidence of ischaemia in ECG in the anterior wall, coronarography was performed with normal findings. No segmental disorders of left ventricular contractility were found, which are typically observed in radiation--induced lesions. The analysis of the distribution of isodoses excluded radiotherapy as a factor influenced cardiotoxicity in all seven cases, and in two patients with clinically manifest cardiac failure the heart was completely outside the radiation rage. In two cases these results suggested a possible connection between epirubicin treatment and cardiotoxicity. These results are presented in Table III and IV.

Lungs

High resolution computed tomography (HRCT) performed after a mean time of 17 months from completion of adjuvant treatment failed to show any changes of the type of postradiation fibrosis in 24 out of 47 patients. In four patients slight changes were present in the apex of the lung (exposed to photon beam from supraclavicular field), in four patients slight parietal fibrotic changes in middle

**Table III. Characteristics of seven patients
with abnormalities in echocardiography examinations**

Chemotherapy: 4x epirubicin + 4x CMF*	6 patients
4 x EC** + 4 x AC***	1 patient
Radiation dose not significant:	
Isodose 50% – outside heart	
Isodose 20% – <10% of the heart	5 patients
Heart outside radiation range	2 patients
Heart function disturbances:	
Disordered left ventricular contractility and one new valvular heart disease	5 patients
Worsening of pre-existant valvular disease	2 patients
Improvement after ACE inhibitor treatment	7 patients

Legend: * CMF - cyclophosphamide, methotrexate, fluorouracil
         ** EC - epirubicin, cyclophosphamide
       *** AC - doxorubicin, cyclophosphamide

**Table IV. Characteristics of two patients with abnormal echocardiography findings without connection
with radiotherapy but with possible connection with chemotherapy**

	Patient 1	Patient 2
Breast side	Right	Left
Chemotherapy: 4x epirubicin + 4x CMF* Total dose of epirubicin	400 mg/m^2	400 mg/m^2
Radiotherapy: Heart volume in radiation range	Heart outside radiation range	Heart outside radiation range
ECG	Lowered V1-V3	Lowered V3-V6
ECHO	LVEF – 53% Global hypokinesis No segmental contractility disturbances	LVEF – 51% Global hypokinesis, left ventricular dilatation, No segmental contractility disturbances
Radioisotope ventriculography	LVEF – 54%	LVEF – 48%
Coronarography	Normal	Not performed

Legend: *CMF- cyclophosphamide, methotrexate, fluorouracil

lobe, near the chest wall (exposed to electron beam from scar area irradiation), and in 15 patients changes were present in the apex and at the chest wall. In summary, there were 19 events in the lung apex and 19 events near the chest wall. Parietal lesions were very slight and involved only a small lung area, fibrosis was also barely discernible and delicate, without lung tissue retraction, in the grade I of progression. They were not visible on any conventional radiograms. Their presence depended on the distribution of isodoses in the lungs. In clinical examinations they could not be detected, produced no symptoms, and were insignificant from the standpoint of survival comfort.

After a mean period of 33 months radiation-induced fibrosis was again studied. HRCT failed to show any changes in 24 patients. Somewhat more frequently apical changes were found in the lungs exposed to radiation (22 vs. 19 in the first examination). The results are presented in Table V. The analysis of the progression of the changes (from stage 0 to 1 or from stage 1 to 2) showed in the group with apical changes, progression in eight cases and regression in four cases. The analysis of the percent of the changes in lung apex in examination I and II was not statistically significant (Mc Nemar' Test p=0.549). In patients with parietal changes, progression was not observed during the follow-up, while the parietal lesions induced by electron beam underwent regression more frequently (6 cases). These differences were statistically significant (Mc Nemar' Test p=0.031)

For evaluation of the intensity of radiation-induced lesions in the lung, conventional radiograms of the lungs were obtained in all cases, beside HRCT. The analysis of the results showed that parietal fibrosis was never detectable, while in eight cases apical changes were found.

No statistically significant relationship was noted between the percent of postradiation fibrosis in the lungs and the type of adjuvant chemotherapy with or without anthracyclines (chi square Test p=0.64). In the group of 40 patients treated with antracyclines, the fibrotic changes were noted in 21 cases and in the group of 7 patients treated with CMF, they were detected in 3 cases.

For assessing the relationship between the dose distribution in the scar and parasternal area and lung fibrosis, the depth of isodose 50% was analysed in this area. In the examination I, in 28 patients without parietal fibrosis, the mean depth of isodose 50% was 1 cm, on average 0-2 cm, and in 19 patients with detectable fibrosis

- the mean depth was 1.9 cm (range 0.5-4 cm). This difference is statistically significant (Kołomogarow-Smirnow Test p<0.05). This observation is important from the standpoint of planned treatment, since in these cases reduction of electron energy, with maintenance of satisfactory dose distribution in the target, should be considered.

Discussion

Heart and radiotherapy

Clinically manifested, adverse effects on the heart are rare events. Literature data on cardiac mortality after radiotherapy was published years ago and was related to radiotherapy techniques no longer used. Their cause was damage to myocardial fibres, myocardial fibrosis, damage to small vessels and coronary arterial narrowing [7, 9-13]. Clinically it is manifested as ichaemic heart disease. The risk of damage depends on the volume of the part of the heart exposed to radiation, type of radiation, size of inlet field, total and fraction doses [7, 9, 10, 14-16]. Radiotherapy to the left side of the chest wall, especially with photons from oblique fields, caused more heart damage (7.9%) than electron beam therapy and/or right chest side irradiation (3.3%) [7, 12, 14, 17]. Consequently, ischaemic heart disease develops after years [14]. In a Swedish study using scintigraphic method Gyenes found, that asymptomatic ischaemic heart disease was 25% more frequent in breast cancer patients receiving radiotherapy to the left breast [7]. Radiotherapy to the left chest side carried out by previous techniques produced damage to three important coronary arteries: left anterior descending, left circumflex, and right coronary artery [12]. Modern radiotherapy methods allow to resolve this problem in most cases, but in certain patients it is not possible to avoid exposure of the left anterior descending artery, and, less frequently, a part of the left main coronary artery [12, 18]. Damage to these arteries leads to ischaemia of the anterior wall of the left ventricle, septum and heart apex [6, 13].

The best way of evaluating radiotherapy-induced cardiotoxicity is perfusion scintigraphy using technetium or thallium, or coronarography, since both these methods allow to assess myocardial blood flow [7, 9, 15]. Irreversible myocardial perfusion defects do not necessarily indicate ischaemic heart disease, but can indicate

Table V. Assessment of fibrosis in irradiated lung in Examination I after a mean period of 17 months and Examination II after a mean period of 33 months in 47 patients

	Examination I 13-28, mean 17 months	Examination II 25-58, mean 33 months
Time of fibrosis detection (mean in months)	17	33
Normal findings	24 – (51%)	24 – (51%)
Apical fibrosis	4 – (8.5%)	10 – (21%)
Parietal fibrosis	4 – (8.5%)	1 – (2%)
Apical and parietal fibrosis	15 – (32%)	12 – (26%)
Total	47 – (100%)	47 – (100%)

myocardial fibrosis after radiotherapy. Such patients have no symptoms of coronary artery disease [9]. Echocardiography permits an assessment of ventricular contractility, myocardial blood flow and the condition of valves. This method is more applicable after chemotherapy, but can also demonstrate segmental left ventricular contractility disturbances typical of radiotoxicity [7, 19].

The present study was carried out in patients receiving 2 Gy fractions to the chest wall from electron beam. Irradiation from oblique fields, especially combined with chemotherapy, is not recommended by the Centre of Oncology in Warsaw. We paid special attention to the correct planning of radiotherapy, using modern equipment and methods.

Heart and chemotherapy

The problem of combined treatment deserves much more attention, especially in the case of anthracyclines. Doxorubicin directly damages myocardial fibres, and cardiomyopathy and congestive heart failure induced by it depend on the cumulated dose [12, 16, 20]. Risk factors for cardiac damage by doxorubicin are: total cumulated dose, old age, history of heart diseases, previous irradiation of heart area or mediastinum, concomitant treatment with paclitaxel or trastuzumab [16]. Circulatory failure caused by doxorubicin develops weeks or months after treatment, mostly after total doses exceeding 550 mg/m^2 [12, 16, 20], although heart failure was reported after doxorubicin dose 40 mg/m^2 [20]. The relative risk of heart damage is 0.1% after low doses, 7% after 550 mg/m^2 dose, and about 50% after cumulative dose 1000 mg/m^2 [11, 12, 20]. In adjuvant treatment of breast cancer patients the total dose is 200 – 360 mg/m^2 which can give 0.1-1% risk of heart failure development [12]. In the Boston study Shapiro et al. evaluated the risk of cardiovascular complications in 299 patients after radiotherapy receiving adjuvant chemotherapy by AC programme (doxorubicin and cyclophosphamide) [14]. The risk of damage was tree to four times higher in patients receiving doxorubicin in 450 mg/m^2 total dose as compared to those given 225 mg/m^2 total dose. A correlation was also observed between the heart volume in radiation area and the risk of heart damage.

In the study of cardiotoxicity degree by echocardiography, Zambetti found abnormalities in 8% of cases, such as left ventricular ejection fraction after doxorubicin, and 1% after treatment with cyclophosphamide, methotrexate and 5-flourouracil [19].

Cardiomyopathy develops in 3% of women treated with trastuzumab, but if it is used in combination with doxorubicin cardiotoxicity rate rises to 18% [16].

No significant adverse effects have been observed after standard cyclophosphamide doses [20]. CMF programme could potentiate cardiotoxicity if administered after radiotherapy to the mediastinum or after previous treatment with doxorubicin [20].

Similarly, 5-fluorouracil only can exceptionally cause cardiac complications (angina pectoris or myocardial infarction), but arrhythmia develops more frequently after this drug [20].

Heart - chemotherapy and radiotherapy

Only few publications have appeared as yet on the risk of late damage to the cardiovascular system following radiotherapy and anthracyclines or taxoids, although cardiotoxic effects of both these drug groups have been well known [16, 20, 21]. It is considered that breast cancer patients treated with doxorubicin and radiotherapy are at increased risk for heart damage [12, 16, 20-22]. There are publications indicating that high doses should be avoided if combined treatment with radiotherapy is given to the left breast or scar area [12, 20, 22].

In patients receiving combined treatment with doxoribicin (total dose 300 mg/m^2) and radiotherapy to the left chest side, 2.6% cases of congestive heart failure were found after a mean time of 6.5 years, while after radiotherapy to the right chest side or no radiotherapy this prevalence of cardiotoxicity was 0.3% [23]. In the retrospective study with M.D. Anderson Cancer Centre 1% cardiotoxicity incidence was found after treatment with doxorubicin 300 mg/m^2 and 4% incidence after 450 mg/m^2 [24]. In another study [23] the percent of patients with acquired congestive heart failure after 7 years of follow-up was: 0% after CMF, 0.8% after CMF with doxorubicin, 2.8% after chemotherapy and radiotherapy to left chest side. Doxorubicin dose 75 mg/m^2 administered in four chemotherapy courses concomitantly with radiotherapy, or doxorubicin dose 450 mg/m^2 given sequentially with radiotherapy increased cardiotoxicity risk [16].

Not all papers report increased frequency of cardiac complications after radiotherapy and anthracyclines. Hendenbergh et al. [25] evaluated the toxic effects of sequential chemotherapy with radiotherapy in 231 patients receiving sparing treatment with doxoribicin 180 mg/m^2 total dose, and cyclophosphamide, methotrexate and 5-fluorouracil with prednisone. During 53 months of follow-up no evidence of heart damage was observed, such as myocardial infarction or congestive heart failure.

The follow-up of patients in the Danish study showed that correctly planned postoperative radiotherapy combined with CMF chemotherapy caused no increase of risk for ischaemic heart disease in 12 years of observation [26]. Similar results were obtained in the Swedish study in which no serious heart damage cases were noted after radiotherapy in the group of 275 patients after a mean follow-up time of 12 years [9].

In the present study six out of seven patients with echocardiographic abnormalities received four courses of epirubicin and four courses of CMF, the total dose of epirubicin was 400 mg/m^2.

Cardiotoxicity after chemotherapy may be manifested as cardiomyopathy or congestive heart failure [14]. In laboratory investigations, abnormalities are found in ECG, LVEF decreased by 50% or more, perfusion defects in coronary arteries, impaired left ventricular systolic and diastolic function, coronary perfusion defects [11, 14, 27].

The percent of patients with subclinical heart damage are not known.

The gold diagnostic standard of evaluation of damage caused by chemotherapy is radioisotope ventriculography and /or myocardial biopsy, but echocardiography is also useful [19, 20]. The patients are evaluated using clinical classification of circulatory failure acc. to NYHA.

Despite the fact that the best method of evaluation of cardiac toxicity after radiotherapy is perfusion scintigraphy white after chemotherapy it is radioisotope ventriculography, we used other methods, which were adapted to the economical possibilities of Cancer Center in Warsaw.

In our study abnormal LVEF in echocardiography was found in two patients: one after radiotherapy to right chest side, the other after left chest side radiotherapy. Both had received four courses of epirubicin and four courses of CMF. No typical signs of radiotherapy-induced damage were found in their case, such as segmental contractility disturbances of anterior wall, septum or heart apex, myocardial infraction or clinical symptoms of coronary artery disease. The analysis of isodose distribution in the heart excluded radiotherapy as the cause of the observed abnormalities. This small number of cases precluded the possibility of analysis of combined treatment effects after radiotherapy to right or left chest side.

No cardiotoxicity of life-threatening degree was noted in our material, but subclinical cardiotoxicity was present in five cases, and NYHA 2 clinical heart failure was detected in two cases. Maybe after a longer follow-up the percent of patients with late complications after combined treatment will increase.

Lungs

High resolution computed tomography (HRCT) is a reliable method for evaluation of the degree of pulmonary fibrosis after radiotherapy [28], allowing for the detection of slight fibrosis and tracking its evolution: progression or involution. The method is highly sensitive, and usually detects lesions before they appear in conventional chest X-ray examination. Pulmonary fibrosis after radiotherapy develops with various frequency, but was reported even in 90% of cases [28, 29]. Usually it produces no clinical symptoms [30]. Fibrosis develops, most frequently, 3 to 18 months after radiotherapy [28, 31] and the most important factor influencing its development is the volume of lung tissue in radiation-covered area and radiation dose in that area [30]. After postoperative radiotherapy or breast conservative treatment with photons from oblique fields pulmonary volume in radiation-covered area is closely correlated with the parameter called central lung distance, which is expressed on radiogram in lateral projection as the distance from the anterior lung border to posterior border of the field. If this distance does not exceed 3 cm the risk of lung damage is low [32]. Skoczylas et al. [33] described the characteristics of apical fibrosis in patients after radiotherapy and chemotherapy or hormonal therapy assessed by means of densitometry. They demonstrated, after analysis of lung X-ray findings, that early pulmonary changes appeared within six months after radiotherapy and had, a tendency for regression, but late fibrosis development after one year remaining most frequently unchanged or rarely showing progression [33].

According to the classification of pulmonary fibrosis in the paper of M. Overgaard et al. [8], in our material in the second examination no changes were present in 24 patients (grade 0). In all patients with parietal changes (13 patients), small disseminated fibrosis foci were found (grade 1). The fibrosis of grade 2, with medium intensity, well visible, rather confluent fibrotic opacities with some retraction of surrounding lung tissue, were observed only in 4 of 22 cases with apical changes. Grade 3 (severe lesion, irregular, confluent, fibrotic lesions in the area exposed to radiation, with high grade retraction of surrounding lung tissue) was never seen. In accordance with the observations of Skoczylas [33] concerning apical fibrosis after photon therapy our results also indicated a tendency for progression or stabilization of lesions in this pulmonary region. A different pattern of changes was noted in parietal fibrosis. These lesions were usually not progressing and some of them undergo even regression after over two years. This could have been due to a relatively low total dose and fractional radiation dose administered to that area.

Conclusions

1. Postoperative radiotherapy as an element of combined adjuvant treatment in breast cancer cases, administered in conventional fractionated doses, causes no clinically significant lesions in the lungs and heart.
2. The analysis of the distribution of isodoses in the heart showed that clinically important myocardial changes observed in two patients were not connected with radiotherapy. Probably they were connected with epirubicin chemotherapy.
3. Correctly planned postoperative radiotherapy is a safe therapeutic method causing no significant disturbances of the functions of vital organs during a mean follow-up period of 33 months.

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