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Preliminary risk assessment of radiation-induced cardiac sequelae in breast cancer patients receiving adjuvant radiotherapy after breast conserving therapy

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Aim of the study. To assess radiation-induced cardiac damage in women with breast cancer irradiated in the course of breast conserving therapy (BCT), basing on electrocardiogram records.
Material and methods. Between January 1985 and December 2002, 656 women with breast cancer treated with BCT received adjuvant radiotherapy at the 1st Department of Radiotherapy of the Maria Sklodowska-Curie Memorial Cancer Center and Institute of Oncology in Warsaw. All patients had pre-treatment electrocardiogram (ECG). Post-treatment ECG was performed occasionally, and routinely in those patients who were seen during follow-up between 2001 and 2002. The study group consisted of 197 patients (103 with tumour of the left breast, 94 with tumour of the right breast) who had at least one ECG performed after radiotherapy. The follow-up period for assessing radiation-induced cardiac damage ranged from 6 to 186 months, mean: 24 mos.
Results. Analysis of ECG records has shown that non specific and/or ischaemic changes were seen in 60 (58%) of patients treated for tumours of the left breast and in 22 (21%) patients treated for tumours of the right breast. The incidence of these changes was threefold higher in patients treated due to tumours of the left breast, as compared to patients with tumours of the right breast. Those ECG changes had no clinical significance – only in three patients, in whom ECG abnormalities were also present before treatment, the heart condition required specific medical treatment.
Conclusions. The results of our study show, that the risk of radiation-induced cardiac damage in breast cancer patients receiving adjuvant radiotherapy after BCT is significantly higher if the left breast is irradiated. The incidence of cardiac damage may be significantly reduced by the use of more precise treatment techniques if the left breast has to be irradiated i.e. radiation beams with strictly limited penumbra. A long follow-up period is required for assessing late radiation-induced cardiac damage.

Wstępna ocena ryzyka powikłań popromiennych ze strony mięśnia sercowego u chorych na raka piersi po oszczędzającym leczeniu chirurgicznym i radioterapii

Cel. Celem pracy jest wstępna ocena powikłań popromiennych ze strony mięśnia sercowego u chorych napromienianych po oszczędzających zabiegach chirurgicznych z powodu raka piersi w oparciu o badania kliniczne i badania EKG.
Materiał i metoda. W Zakładzie Radioterapii I Centrum Onkologii – Instytutu od 2 stycznia 1985 r. do 30 listopada 2002 r. napromieniano 656 chorych na raka piersi po oszczędzającym leczeniu chirurgicznym. Wszystkie pacjentki miały wykonane badanie elektrokardiograficzne przed rozpoczęciem leczenia. Kontrolne EKG wykonywano okazjonalnie, natomiast rutynowo u pacjentek kontrolowanych w latach 2001–2002. Badana grupa obejmowała 197 pacjentek, u których wykonano przynajmniej jedno badanie EKG po radioterapii. Okres obserwacji zmian popromiennych w mięśniu sercowym wahał się od 6 do 186 miesięcy (średnio 24 miesiące). Guz piersi lewej stwierdzono u 103 pacjentek, prawej u 94.
Wyniki. Zestawienie wyników EKG wykazało, że niespecyficzne zmiany zapisu lub zmiany niedokrwienne wystąpiły u 58% chorych leczonych z powodu raka piersi lewej i u 21% chorych na raka piersi prawej. Należy podkreślić, że zmiany niedokrwienne w mięśniu sercowym stwierdzano ponad 3-krotnie częściej po leczeniu nowotworów piersi lewej. Zmiany miały charakter subkliniczny, tylko w trzech przypadkach, w których zmiany zapisu występowały również przed leczeniem, wystąpiły zaburzenia wymagające leczenia i opieki kardiologicznej.

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Wnioski. Uzyskane wstępne wyniki zdecydowanie wskazują na zwiększone ryzyko uszkodzeń serca po leczeniu napromienianiem na obszar piersi lewej. Liczbę powikłań kardiologicznych można by w znacznym stopniu zmniejszyć w wyniku stosowania bardzo precyzyjnej techniki planowania leczenia oraz stosowania wiązek promieniowania o ostro ograniczonym półcieniu. Konieczność długotrwałej obserwacji tych przypadków wymaga kontynuacji pracy.

Key words: breast cancer, breast conserving therapy, radiotherapy, radiation-induced heart disease
Słowa kluczowe: rak piersi, leczenie oszczędzające, radioterapia, powikłania kardiologiczne

Introduction

The number of patients irradiated for breast cancer has, in the recent years, increased significantly. This phenomenon arises from the rising popularity of breast conserving therapy (BCT), of which irradiation is a necessary element. We have also been observing this increase at the Dept. of Radiotherpy of the Maria Sklodowska-Curie Memorial Cancer Center and Institute of Oncology in Poland. Between January 1985 and November 2002 we had irradiated 656 patients in the course of BCT for breast cancer.

Radiotherapy applied for breast cancer carries a number of risks, of which the possibility of developing myocardial ischaemia is the most serious, leading, in course, to increased mortality caused by ischaemic heart disease. The first report concerning a possible increase in mortality arising from cardiac damage as a late complication of radiotherapy was published by Haybittle in 1989 [1]. He reported an increased risk of cardiac complications in patients irradiated after radical mastectomy. This finding was later confirmed in the course of randomized studies and in meta-analyses performed by Cuzick et al [2]. Conclusions from these reports advise the use of techniques, which provide maximal reduction of the dose applied to the heart, especially in patients with good prognosis and estimated long survival. Most authors provide data suggesting that the period of greatest risk of cardiac death begins 7 years after irradiation, reaches its peak in the second decade after treatment and then gradually decreases [1, 3, 4]. It has been shown that irradiation of the left side of the chest increases the risk of cardiac death by 20%, as compared to the risk in patients irradiated on the right side of the chest [5, 6]. In patients in whom the entire heart volume has been irradiated cardiac mortality reaches approx. 4.7-6.8% [7]. Naturally, the heart volume irradiated in the course of BCT is significantly smaller. Geynes et al. have estimated that in the course of 50% isodose irradiation from diagonal fields only some 5.7% of the entire heart volume is irradiated [8], in which case the risk of cardiac damage remains at the level of 1% [9]. Most authors report relatively high ratios of heart damage caused by irradiation for breast cancer. However, these damages are, in a majority of cases, subclinical. These signs of damage may be observed in the course of different investigations [10-13]. At present there is no detailed data concerning minor cardiac damage, while at the same time it is very likely that radiotherapy may be responsible for milder forms of ischaemic heart disease. In view of the already high and persistently increasing number of patients with breast cancer, who undergo BCT we have attempted to evaluate the risk of developing radiotherapy-induced cardiac damage. Such an analysis is all the more valuable because patients qualifying for BCT have good prognosis and are likely to achieve long survival. This paper presents the results of a pilot study, which we intend to perform on a much larger scale. It has been designed in order to perform a generalised, initial evaluation of the frequency and range of possible cardiac damage arising from irradiation. It is important to stress that all our patients presented with initial electrocardiograms routinely performed before general anaesthesia. This is one of the reasons why for our diagnostic tool we have chosen electrocardiography, even though it has neither the highest sensitivity nor specificity. The ECG is also the simplest and the most available method of evaluating possible cardiac damage. Only in selected cases did we refer our patients for echocardiography and myocardial perfusion imaging.

Material and methods

Between January 2000 and November 2002 we had performed control follow-up evaluation of 206 patients irradiated previously in the course of BCT. The evaluation consisted of case history, routine physical examination and, in 197 patients (103 irradiated on the left side of the chest and 94 – on the right) – systematically performed ECG. The length of follow-up from the end of irradiation varied between 6 and 186 months (mean time – 24 months) – 45 patients were observed for over 5 years and 10 for over 7 years.

ECG was performed before the onset of therapy and at different time points after irradiation. The changes observed in ECG were pronounced as non-specific – abnormalities of repolarization in the V1-V3 leads (abnormalities of the ST-T wave with low-voltage or isoelectric T wave). In 44 cases ECG revealed signs of ischaemia of a variable extent. We used the chi square test to evaluate the statistical significance of the obtained results; to calculate the probability of survival free of ECG abnormalities we used the Kaplan-Meier method, while the differences observed between patients irradiated on the left side of the chest and the right side of the chest was calculated with the log-rank test with the significance level set at 0.05. Examples of non-specific and ischaemic abnormalities in the ECG are presented on Figures 1 and 2.

Results

ECG results are presented in Table I.

Only in 3/197 patients did we observe clinically relevant symptoms of heart damage (with specific signs observed in the ECG) demanding cardiological treatment. In two cases radiotherapy caused exacerbation of

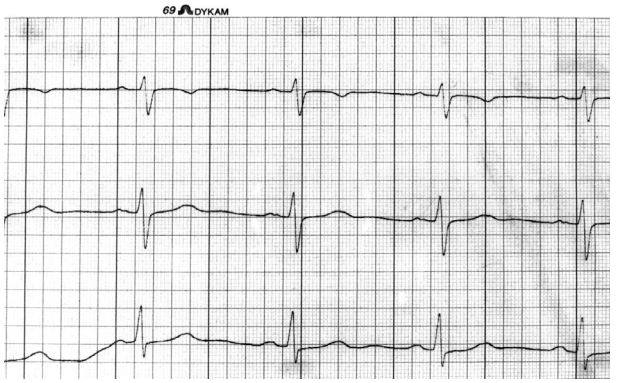

Figure 1A

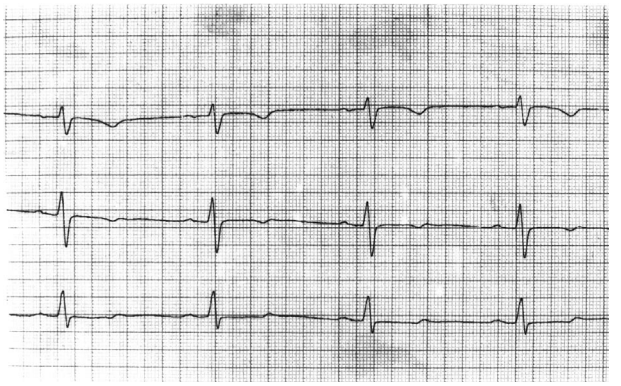

Figure 1B

Figure 1. A. ECG before treatment – normal; B. ECG after treatment – nonspecific abnormalities

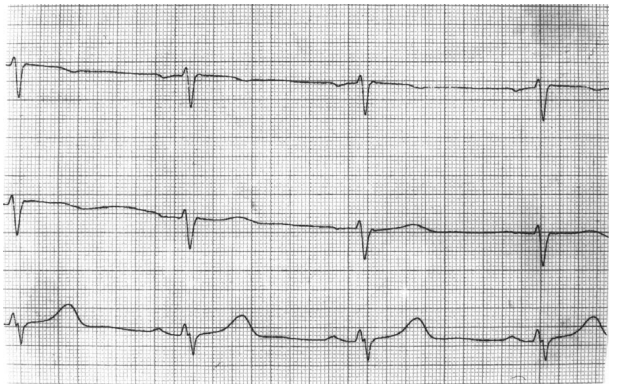

Figure 2A

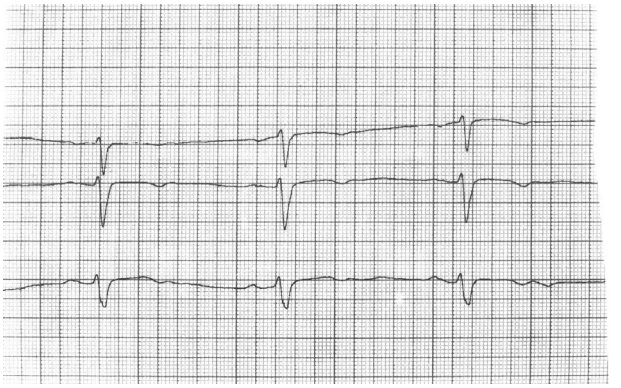

Figure 2B

Figure 2. A. ECG before treatment – normal; B. ECG after – ischaemic changes

Table I. ECG results of 197 patients irradiated in the course of breast conserving therapy

ECG results	Left breast (%)	Right breast (%)
No abnormalities after irradiation	38 (36.7%)	56 (60%)
ECG abnormalities observed before irradiation	5 (5%)	16 (19%)
Abnormalities observed after irradiation	60 (58%)	22 (21%)
– non-specific	23 (22%)	11 (12%)
– ischaemic	34 (33%)	10 (9%)
– clinically evident (demanding treatment)	3 (3%)	0
Total	103	94

ischaemic heart disease also calling for specific treatment. In these two cases we observed ECG abnormalities prior to irradiation, although the patients were symptom-free. One patient, in whom prior to treatment we observed a significantly slow sinus rhythm, underwent myocardial infarct 6 months after the termination of radiotherapy. However, the infarct did not leave any permanent changes in the ECG and no persistent clinical manifestations. In 21 cases ECG abnormalities were already present before the onset of irradiation. Among these patients irradiation did not cause either exacerbation of ECG abnormalities nor of clinical symptoms. In the case of all other patients the ECG abnormalities were subclinical and no complaints were reported.

Ten patients irradiated on the left side of the chest received concomitant chemotherapy – four of these were treated with the AC programme. In two of them we observed no ECG abnormalities, in one non-specific changes were observed and in one we observed ischaemic changes, which were also discernible before the onset of treatment. The remaining six chemotherapy patients were treated according to the CMF programme. In four of them we observed non-specific ECG abnormalities, in two – extensive signs of ischaemia. Among the patients irradiated on the right side of the chest only four received concomitant chemotherapy: three according to the CMF programme and one according to the AC programme. No ECG abnormalities were observed in any of them.

Table II. A comparison of the ratio of post-irradiation ECG abnormalities observed in the course of breast conserving therapy (BCT) at the 1st Department of Radiatherapy of the Maria Sklodowska-Curie Memorial Cancer Centre with similar results reported by other centers

Center	Treatment modality	Ratio of observed ECG abnormalities left breast	right breast
Radiumhemmet Stockholm; 1994 data [11]	RT	25%	0%
Radiumhemmet Stockholm; 1996 data [9]	RT	50%	-
Dept. of Radiation Oncology; Durham NC, USA [10]	RT + CHTH RT	60% 50%	- -
Dept. of Radiology, Royal Marsden Hospital, London [12]	RT	71%	17%
1st Dept. of Radiotherapy, Institute of Oncology, Warsaw, Poland	RT	58%	21%

RT – radiotherapy
CHTH – chemotherapy

Post-irradiation ECG abnormalities were observed in 58% of patients treated for cancer of the left breast and only in 21% of patients treated for cancer of the right breast.

The difference in the frequency of ECG abnormalities after irradiation for cancer of the left breast and of the right breast reaches high statistical significance (chi-square 24.10 for $p = 0.001$). It is also necessary to stress that abnormalities characteristic of ischaemia were three times more frequent among patients irradiated for cancer of the left breast. The probability of survival free of ECG abnormalities in relation to tumour localization is presented in Figure 3. The observed differences are statistically highly significant ($p = 0.006$).

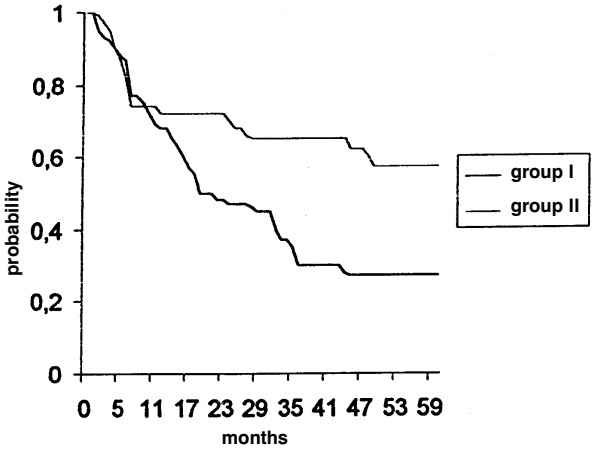

Figure 3. Probability of survival free of ECG abnormalities after irradiation of the left (group 1) and the right (group 2) side of the chest

Discussion

In a pilot study of cardiac damage in women irradiated for breast cancer ECG abnormalities were found to be more common among patients irradiated on the left side of the chest.

These observations are also confirmed by other authors and in Table II we have compared our results with those reported from other centers. Most of the cited reports use dynamic isotope methods of discerning cardiac damage, thus reporting such changes as subclinical abnormalities found in visualized perfusion studies and myocardial ischaemia. However, a precise comparison of the results reported by different centers is very difficult due to different techniques of treatment planning and the variations in treatment fields which they cause. One of the crucial elements to be considered in treatment planning is the maximum area of the heart wall (i.e. the width of the heart as seen on the testing projection picture from the simulator) which will remain within the irradiated field. The distance between the most outward part of the heart outline and the edge of the irradiated field as seen on the testing projection picture from the simulator correlates well with the irradiated heart volume (Figure 4). Hurkmans et al. used this very parameter to calculate the risk of heart damage acc. to their own developed model [4, 9]. If this distance is less than 1.5 cm

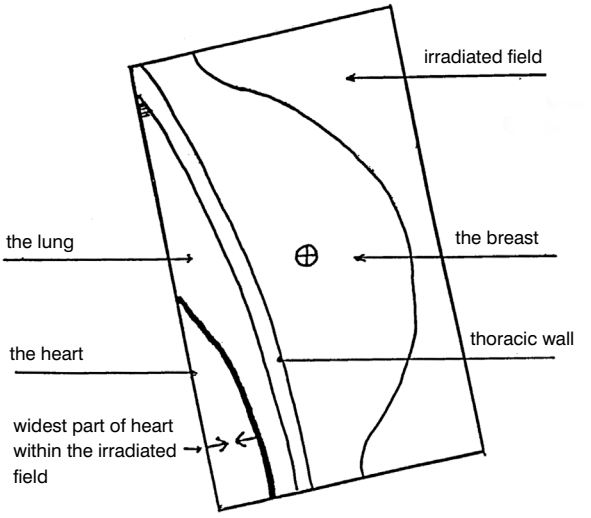

Figure 4. Schematic picture of the heart and lung volumes within the irradiated field – side projection

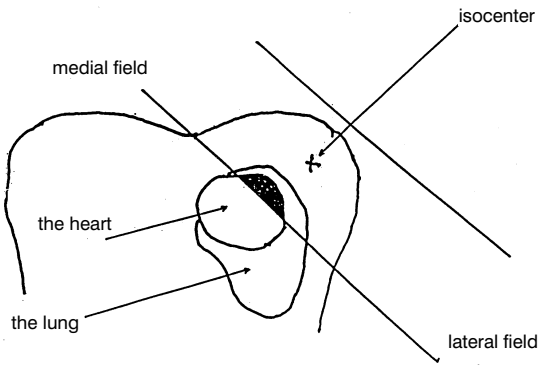

Figure 5. Diagram showing a cross section obtained during computer treatment planning – the heart volume found within the irradiated field discernible in the lower part of the field

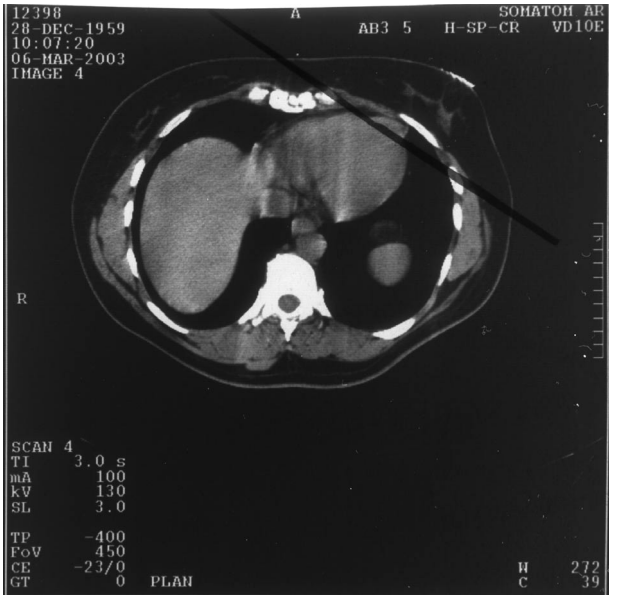

Figure 6. CT scan of the lower part of the irradiated field

– the risk of cardiac damage remains below 1%. Their calculations were performed for a dose of 50 Gy given in 25 fractions with no concomitant systemic chemotherapy. Other authors maintain, that the aforementioned distance should not exceed 1 cm, however it is not always technically possible to altogether avoid applying radiation to the heart. The standard procedure is to use two oblique fields, in case of which the entire elimination of the heart from the irradiated area is difficult (Figure 5). The presence of a part of the heart volume within the irradiated area is confirmed on the CT scan of the lower part of the field (Figure 6). Fuller et al. stress that even providing modern techniques and careful treatment planning the left descending artery and the area of its supply (the anterior wall of the heart) may receive a relatively high radiation dose [14]. Gogliardi and Magee have shown that due to anatomical variations of the heart's position in approximately 9% of cases it is impossible to avoid its irradiation [15, 16].

Precise treatment planning is of extreme importance. It should include corrections arising from the testing projection pictures taken on the simulator, from isodose graphs and from CT scans. An example of such corrections is presented on Figure 7. According to the first version of the myocardium would receive a significant radiation dose. After corrections the isodose crossing the myocardium has only a 10% dose value. In the course of our studies we have found that in 34% of cases it is possible to completely eliminate the heart from the irradiated field providing that the initial heart volume at risk of irradiation is estimated from the simulator scans. Irradiation with the acceptable dose was possible in 40% of cases, while in the remaining 26% of cases it was impossible to reduce the size of the irradiated part of the heart below 2-3 cm.

Conclusions

The initial results prove that the risk of post-radiotherapy heart damage is increased after irradiation of the left breast.

The number of cardiac complications may be significantly reduced by decreasing the dose applied to the heart which is possible with precise treatment planning

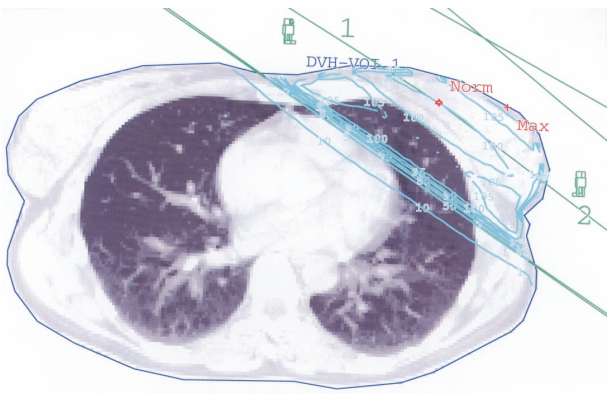

Figure 7A

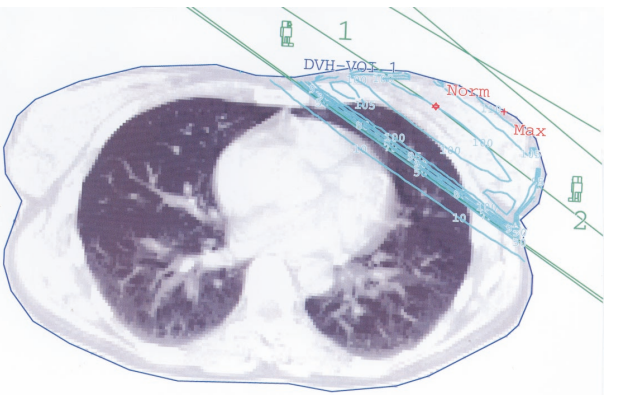

Figure 7B

Figure 7. A. Treatment planning – myocardium within range of the beam; B. Same patient – treatment planning after corrections – myocardium only within range of the 10% isodose

and the use of radiation beams with strictly limited penumbra.

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