Acta Radiologica Oncology 22 (1983) Fasc. 6

FROM THE DEPARTMENT OF CLINICAL PHYSIOLOGY, RADIUMHEMMET, AND THE DEPARTMENT OF HOSPITAL PHYSICS, KAROLINSKA SJUKHUSET, S-10401 STOCKHOLM, SWEDEN.

ELECTROCARDIOGRAPHIC CHANGES AFTER RADIATION THERAPY FOR CARCINOMA OF THE BREAST

Incidence and functional significance

J. LINDAHL, L.-E. STRENDER, L.-E. LARSSON and A. UNSGAARD

Since the 1920s, treatment by irradiation of various thoracic malignancies such as carcinoma of the breast, lung and oesophagus has been reported to cause side effects by damage to the heart and lungs (JONES & WEDGWOOD 1960, COHN et coll. 1967, RUBIN & CASARETT 1968, GROSS 1977). Several case reports on serious complications from the heart such as pericardial effusion, perimyocardial fibrosis and myocardial infarction have appeared.

Changes in the electrocardiogram which may indicate myocardial damage have been reported, including arrhythmias, conduction defects and T-wave abnormalities. However, the incidence of the changes reported has varied, from 8 per cent (BIRAN et coll. 1969) to 100 per cent (COOPER 1967), for instance, in treatment for carcinoma of the left breast, and the materials have been small. In addition, no systematic analysis of the functional significance of these ECG changes seems to have been made.

By megavoltage roentgen and electron therapy and by ^{60}Co therapy larger doses can be delivered to deep structures and by improved dose planning less damage to structures adjacent to the tumor can be accomplished. To evaluate the rate and type of ECG changes induced by the present technique of irradiation and to determine their effect on physical working capacity, a major series of patients referred for treatment of breast carcinoma by irradiation were examined before, and two and six months after treatment. Subsequently, a follow-up investigation to determine the long-term consequences has been initiated.

Material and Methods

During a period of about two and a half years 197 unselected female patients with primary carcinoma of the breast were included in this investigation. Of these patients, 190 had an operable carcinoma and received adjuvant radiation therapy, and 7 patients were not operable because of a locally advanced primary tumor. The diagnosis was confirmed by fine needle biopsy cytology (FRANZÉN & ZAJICEK 1968). All patients were referred to Radiumhemmet for the treatment. Patients were allocated to the different treatment groups according to the opinion of the radiotherapist in charge of the patient. The seven patients with advanced local disease were treated with irradiation only. The number of patients, their ages, and the treatment groups appear in Table 1.

Radiation therapy. The various modes of treatment are described anatomically in Table 1.

Irradiation as the only means of treatment or as preoperative treatment was physically administered in the same way, and differed only in magnitude of total radiation dose to the tumor region. The major-

Accepted for publication 22 August 1983.

Table 1

Patient material and radiation treatment. The irradiation was given with conventional fractionation

Mode of treatment and irradiated region	No. of patients	Age in years		Affected breast		Total tumor dose (Gy)	Duration of treatment in days
		Mean	Range	Right	Left		
Irradiation only (full dose treatment) Breast (including homolateral internal mammary chain) Regional lymph nodes (axilla, infra- and supra-clavicular fossae)	7	56	49–65	2	5	64–70	34–70
Preoperative irradiation Breast (including homolateral internal mammary chain) Regional lymph nodes (axilla, infra- and supra-clavicular fossae)	68	54	32–70	37	31	40–48	26–50
Postoperative irradiation Chest wall (including homolateral internal mammary chain) Regional lymph nodes (axilla, infra- and supra-clavicular fossae)	98	54	33–75	48	50	36–56	17–55
Parasternal region only	24	58	34–75	14	10	24–46	16–41

ity of these patients were irradiated with a ^{60}Co unit. A few patients, however, were treated with linear accelerators (roentgen beam).

Postoperative irradiation to the chest wall was given either with high energy electrons or with ^{60}Co units in the same way as for preoperative irradiation but with the irradiated volumes adjusted to the thinner target volume with the breast removed. Parasternal irradiation was given with a ^{60}Co unit and a short source–skin distance (6 cm).

For all patients except those receiving irradiation to the parasternal region only, individual treatment plans were made showing the dose distribution within the region of interest and with consideration taken to the extent of the tumor and to body contour, chest wall thickness and other anatomic factors.

Irradiation of the axilla and clavicular fossae does not significantly contribute to the radiation dose to the heart and thus was not considered.

Schematic drawings of treatment plans for preoperative irradiation with a ^{60}Co unit and postoperative irradiation with electrons are presented in Fig. 1.

The postoperative irradiation of the parasternal region was administered according to a standard scheme with a series of treatments with small fields (3.5 cm × 6 cm) as a chain with the aim of giving 42 Gy at the surface of the sternum.

The electron energies used were determined by the thickness of the chest wall in such a way that the inner surface of the chest wall would receive a radiation dose that was 95 per cent of the tumor dose.

On the basis of the individual treatment plans, the mean radiation doses to the anterior wall and to the anterior quarter and half of the heart were calculated for each patient.

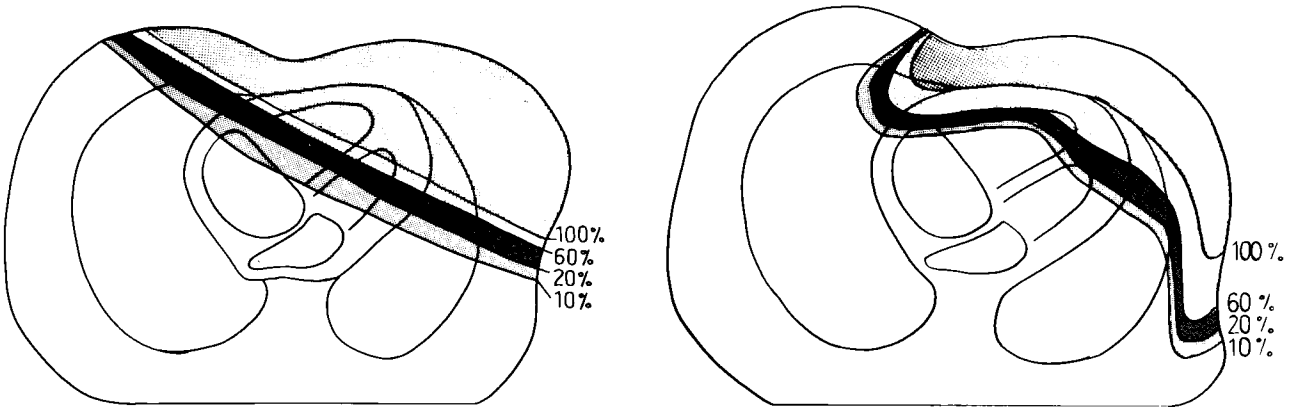
The radiation given for carcinoma in the right breast gave, for obvious reasons, lower mean doses to the heart although the medial and right part of the heart could be included in the primary radiation beam(s).

For those patients who received irradiation in accordance with the plan in Fig. 1 a, the mean doses to the parts of the heart mentioned above varied within a factor of two. Where electron irradiation

Table 2

Number of patients in the total material with various ECG abnormalities before and after radiation therapy. Classification according to the revised Minnesota code (ROSE & BLACKBURN)

Type of ECG item	Minnesota ECG code	At rest supine			During and/or after exercise		
		Before therapy n=197	Two months after end of therapy n=186	Six months after end of therapy n=180	Before therapy n=172	Two months after end of therapy n=160	Six months after end of therapy n=157
Q waves	1 1–3	4	4	4	2	3	3
QRS axis	2 1–5	2	4	4	2	2	2
High ampl. R wave	3 1–3	1	1	1	1	1	1
ST-depression	4 1–4	15	14	15	45	44	48
Major depression	4 1–3	12	12	12	12	14	17
Minor depression	4 4	3	2	3	33	30	31
T-wave items	5 1–4	22	33	61	17	30	47
A-V conduction	6 1–5	1	1	2	1	1	1
Ventr. conduction defects	7 1–6	4	3	4	4	3	3
Arrhythmias	8 2–9	6	10	13	0	0	0
Miscellaneous	9 1–5	0	0	0	0	0	0
Ectopic beats	10 1–8	6	7	8	28	29	32
Ventricular	10 1–5	5	6	5	15	21	16
Supraventricular	10 6–8	1	1	5	15	11	19



a b

Fig. 1. Plans for irradiation in connection with breast carcinoma. The figures indicate the borderline of the percentage tumor doses. a) Full dose and preoperative irradiation of the left breast with a ^{60}Co unit. b) Postoperative irradiation with electrons (12 MeV) of the left chest wall.

was used, the mean doses to the heart varied considerably, however, mainly increasing with electron energy and decreasing when special tissue equivalent material (bolus) was used to compensate for variations in chest wall thickness. Parasternal irradiation gave the patients a mean dose of 14 Gy to 17 Gy to the anterior half of the heart.

Design of the investigation. Physical examination, an exercise test with ECG, and radiography for determination of heart volume were performed before radiation therapy, and two and six months after completion of the treatment. In the patients who received parasternal irradiation no exercise test or heart volume determination was included. Surgery was performed about 5 weeks before the first examination in the postoperative group and about 6 weeks before the second examination in the preoperative group.

Physical examination. At the radiation therapy department, each patient was examined by the phy-

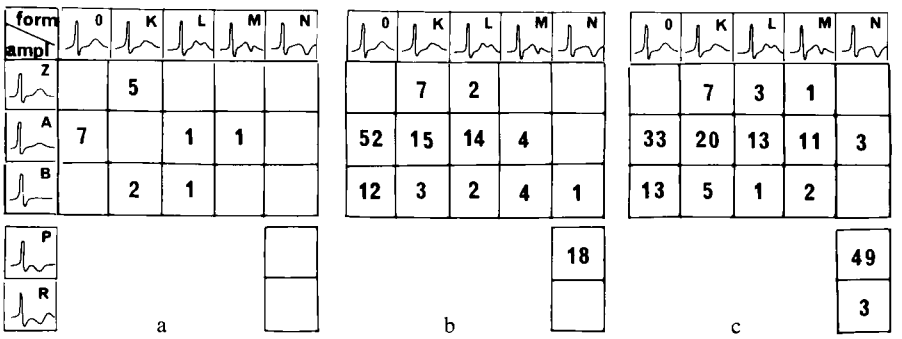


Fig. 2. ECG T-wave abnormalities at rest in precordial leads V_2, V_4 and V_5 before (a), 2 (b) and 6 (c) months after end of radiation therapy. The T-wave abnormalities were classified as illustrated in each of these leads separately and reported in the figure (ATTERHÖG & MALMBERG). The number of patients was 197, 186 and 180, respectively. (ECG illustrations are reproduced with permission of the Clinical Cardiology Publishing Co.)

sician supervising the treatment and a history was taken with particular reference to cardiovascular and pulmonary symptoms. During the treatment period the patients were examined and questioned about such symptoms once a week. The majority of the patients were seen by the same physician.

An *electrocardiogram* was recorded with a Mingograf 61 or 81 (Siemens Elema, Solna, Sweden). A conventional 12-lead ECG was recorded at rest with precordial leads as both V and CR leads. During exercise, chest-head leads were recorded. An ECG was recorded on each load as well as 0, 4 and 10 minutes after exercise and in addition continuously at low paper speed before, during and for 10 minutes after exercise for detection of arrhythmia. All ECG abnormalities were classified according to the revised 'Minnesota code' (ROSE & BLACKBURN 1968; Table 2). The same code was used for resting ECG as for ECG during and after exercise. Changes from rest to exercise were not coded as such but resting and exercise ECGs were coded independently. In each instance the most severe changes were reported. For a detailed classification of ectopic beats an additional category 10: 1–8 was included (ÅSTRAND et coll. 1967). Ectopic beats were not reported, however, if only one supraventricular or ventricular ectopic beat, or one of each, was recorded on the entire resting and exercise ECG.

In addition, T-wave abnormalities in precordial leads V_{2-5} were classified according to ATTERHÖG & MALMBERG (1981), where T-waves are characterized by amplitude criteria and notch criteria as illustrated in Fig. 2. The amplitude criterion A (low amplitude) was modified here to include also a reduction of the T-wave amplitude by more than 50 per cent compared with the pretreatment ECG.

Exercise tests were performed on electrically braked bicycle ergometers (Siemens Elema) with stepwise increased 6 minute loads (SJÖSTRAND 1960). The test was interrupted when the patient reached a heart rate of 170 beats/min or had to stop because of general fatigue or other subjective complaints. Physical working capacity was expressed as the work load at heart rate 170 beats/min (PWC 170).

Heart volume was determined roentgenologically in the prone position according to KJELLBERG et coll. (1951).

Statistical calculations were performed according to standard methods as outlined by SNEDECOR & COCHRAN (1967). Statistical significance was calculated by Student's t-test of paired and unpaired samples, as appropriate.

Each patient gave an informed consent to participate in the investigation, which was approved by the Ethical Committee of the hospital.

Results

Subjective symptoms. A deterioration in general condition during radiation therapy was reported by 67 per cent of the patients in the preoperative group and 40 per cent in the postoperative group. Two months after treatment the corresponding figures were 51 and 21 per cent, respectively, with further improvement six months after treatment. Shortness of breath and palpitation of the heart were reported by about 10 per cent of the patients in both groups before treatment with an increase to about 30 per cent in the preoperative group and 15 per cent in the postoperative group two and six months after treatment.

Table 3

Physical working capacity expressed as work load at heart rate 170 beats/min (PWC 170) before and after irradiation. Statistically significant changes compared with pretreatment figures are indicated

	Physical working capacity, PWC 170, watt (mean ± SD)		
	Before therapy	Two months after end of therapy	Six months after end of therapy
Preoperative irradiation (incl. full dose treatment)	112±26 n=70	103±25 n=61 p<0.001	106±25 n=60 p<0.05
Postoperative irradiation	104±21 n=87	104±25 n=78	104±23 n=75
Total material	108±24 n=157	104±25 n=139 p<0.01	105±24 n=135

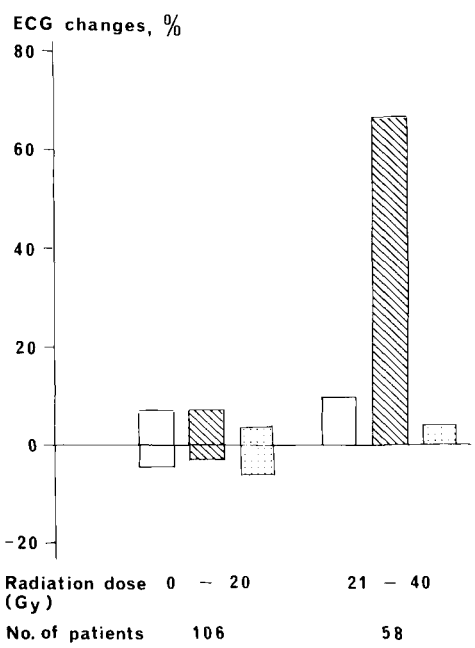


Fig. 3. ECG changes at rest in the total material 2 months after irradiation compared with the ECG before treatment and related to mean radiation dose to the anterior quarter of the heart. Zero means no change compared with ECG before irradiation. ECG abnormalities separated into arrhythmias and ectopic beats (unshaded) T-wave abnormalities (hatched) and miscellaneous ECG abnormalities (dotted).

Edema, extrasystoles and chest pain were reported by about 5 per cent of the patients before treatment, with a slight increase after treatment.

With irradiation of the parasternal region only, 20 per cent of the patients reported deterioration in general condition during and after treatment and no increase in the symptoms mentioned above.

No correlation existed between appearance of subjective symptoms after radiation therapy and the radiation dose to the heart.

ECG abnormalities. Before radiation therapy ECG abnormalities were recorded in 21 per cent of the patients at rest and in 44 per cent during or after exercise.

Two and six months after treatment ECG abnormalities were recorded in 30 and 47 per cent of the patients at rest and in 48 and 58 per cent during or after exercise. The numbers of different ECG items were almost the same as before treatment. The only exception was the increase in T-wave abnormalities two months and particularly six months after treatment (Table 2). Hypertension with left ventricular strain and digitalis glycosides may have contributed to the ST-T abnormalities in 5 and 8 patients, respectively.

The more sensitive classification of T-wave abnormalities by the system of ATTERHÖG & MALMBERG revealed the incidence of precordial T-wave changes already two months after treatment (Fig. 2). T-wave changes appeared in 35 per cent of the patients. Six months after treatment the number of patients with T-wave changes was about the same as at two months after treatment but the changes were more marked.

The flattening, deformity or inversion of the T-wave usually was of the same magnitude in leads V_2 and V_4 and less severe in lead V_5, usually exhibiting a reduced T amplitude only.

Thus, the only significant ECG change after radiation therapy was an increase in T-wave abnormalities in leads reflecting the anterior wall of the heart. These ECG changes were correlated to the radiation

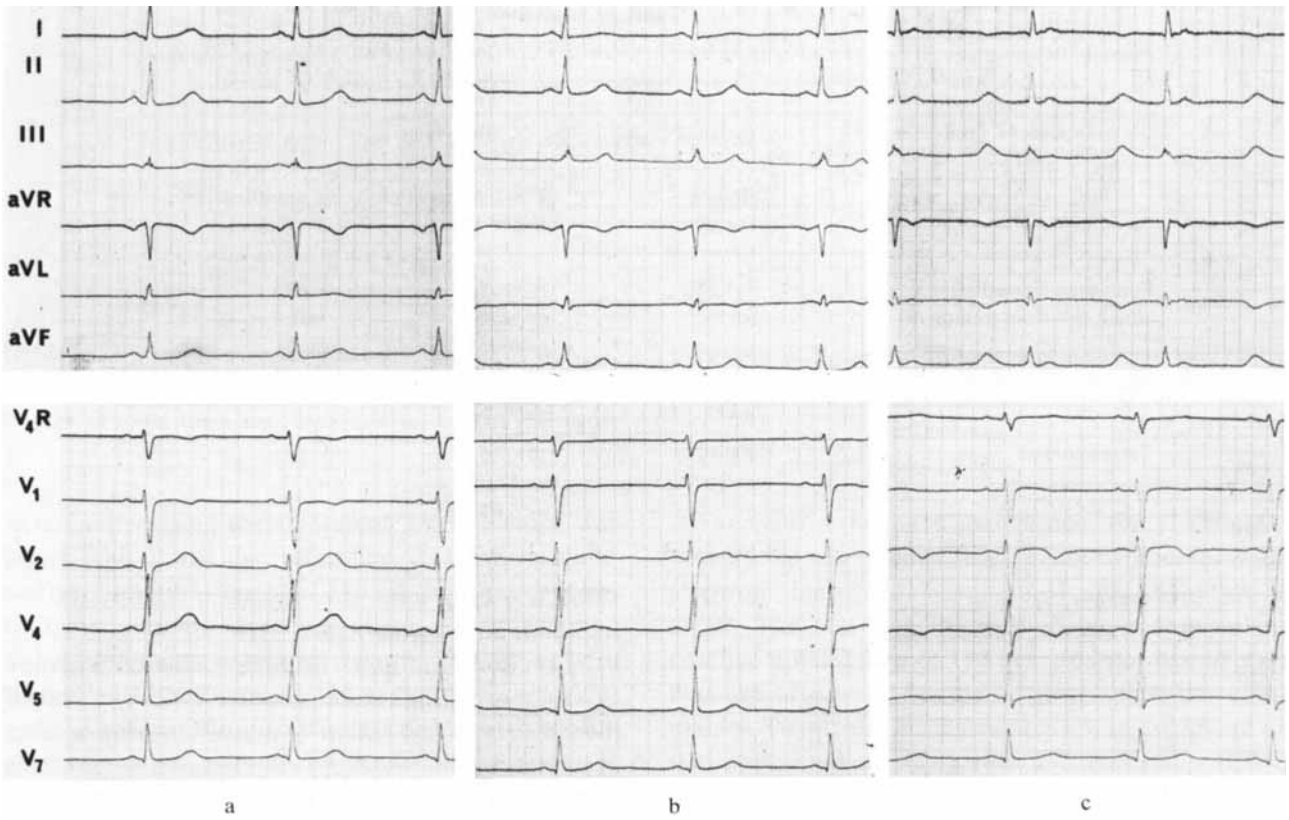


Fig. 4. ECG recorded in a 48-year-old woman before (a), 2 (b) and 6 (c) months after postoperative radiation therapy for carcinoma of the left breast, illustrating the T-wave changes.

Table 4

Heart volume before and after radiation therapy. Statistically significant changes compared with pretreatment figures are indicated

	Heart volume, ml (mean ± SD)		
	Before therapy	Two months after end of therapy	Six months after end of therapy
Preoperative irradiation (incl. full dose treatment)	610±144 n=70	617±144 n=63	629±153 n=62
Postoperative irradiation	617±119 n=92	632±122 n=86 p<0.05	656±135 n=83 p<0.01
Total material	614±132 n=162	626±133 n=149	644±144 n=145 p<0.01

dose absorbed by the heart, appearing in 8 per cent of patients receiving up to 20 Gy and in 74 per cent of those given more than 20 Gy to the anterior quarter of the heart (Fig. 3). The T-wave changes are illustrated by the ECG in Fig. 4.

Physical working capacity. PWC 170 was on an average 108 W before radiation therapy, decreased slightly to 104 W ($p<0.01$) two months after treatment and to 105 W six months after treatment (Table 3). The average PWC 170 before radiation therapy was higher in patients with preoperative treatment than in patients with postoperative treatment.

PWC 170 was significantly reduced ($p<0.001$) two months after treatment in the former group, while in the latter group it was unchanged compared with the situation before irradiation.

At the exercise test, the patients had to stop due to subjective symptoms in about 70 per cent of the tests. The major subjective symptom reported was general fatigue and fatigue of the legs in most cases and breathlessness in less than 10 per cent of the tests, with little difference between the three examinations. The test was interrupted as the patient reached a heart rate of 170 beats/min in about 30 per cent of the tests and because of other causes, such as an ECG reaction or blood pressure reaction, in a few instances only.

No correlation existed between reduction in PWC 170 after radiation therapy, and the age of the patient, radiation dose to the heart, or appearance of ECG T-wave changes after treatment.

Heart volume. The heart volume was on an average, for the whole patient group, 614 ml before, 626 ml two months after, and 644 ml six months after therapy (Table 4). In the preoperative group, heart volume was unchanged while in the postoperative group it increased from 617 ml before, to 656 ml six months after treatment ($p<0.01$).

The heart volume increased by 225 ml in one patient and 450 ml in another, but without signs or symptoms of pericardial effusion or cardiac decompensation. It decreased by 275 ml in another patient but otherwise all changes in heart volume were less than 200 ml. Pericarditis was diagnosed clinically in one patient only, in whom a pericardial friction rub was heard and ECG T-wave changes were recorded, but the patient had no symptoms and no change in heart volume or physical working capacity.

No correlation existed between change in heart volume after radiation therapy, and the age of the patient, radiation dose to the heart, or appearance of ECG T-wave changes after treatment. Further, no correlation was noted between change in heart volume and change in physical working capacity.

Discussion

The prevalence of ECG abnormalities before treatment in the present material was less than that reported for subjects of the same age and sex in a health survey in Stockholm (JONSSON & ÅSTRAND 1977). The difference lies essentially in the frequency of ST depression reported, a difference that can be explained at least in part by the use of the revised edition of the Minnesota code in the present series. The incidence of T-wave changes after radiation therapy is in agreement with that of CATTERALL & EVANS (1960) in a small series, but lower and higher figures have also been reported (COOPER, BIRAN et coll.). No increase in arrhythmias or ectopic beats was noted in the present material, which is in agreement with the experience of LEACH (1943), among others.

The T-wave changes occurred essentially after left-sided pre- or postoperative irradiation, where the dose to the anterior part of the heart usually exceeded 20 Gy. Among these patients the incidence of precordial T-wave changes was the same in the preoperative and the postoperative group (74–75%) in spite of a higher average mean radiation dose to the anterior quarter of the heart in the preoperative group (36 vs. 30 Gy). An increase in T-wave amplitude after mastectomy (LAMONTE & FREIMAN 1965) might have reduced the difference between the first and second examination and the number of reportable T-wave changes in the preoperative group after irradiation and surgery.

Low or inverted T-waves in precordial V leads are found also in healthy persons. The T-wave changes reported in the present series appeared in comparison with the pretreatment recordings. Further, the same pattern of T-wave changes appeared in the CR leads, where T is normally positive (DEEDS & BARNES 1940), indicating that the T-wave changes reported were not the result of variability of the T-waves in V leads.

The CR T-wave changes were less marked in CR_1 than in CR_{2-4}, suggesting that they represented a perimyocardial radiation reaction rather than right ventricular strain due to radiation pneumonitis and pulmonary hypertension.

The radiation therapy and the appearance of ECG T-wave abnormalities did not significantly affect physical working capacity. No previous report seems to have been published where the functional significance of the ECG T-wave abnormalities appearing after radiation therapy has been systematically analyzed. Considering the subgroups, a lower PWC 170 was noted after irradiation plus mastectomy in the preoperative group, and after mastectomy but before irradiation in the postoperative group, but no further reduction after irradiation alone in the latter group. Thus, physical working capacity seemed to be reduced as a consequence of operation

rather than of irradiation, despite considerable time for recovery after surgery (ADOLFSSON 1969).

Clinically, only one case of pericarditis was diagnosed. A large increase in heart volume was recorded in 2 other patients, but none of them had symptoms from the heart and physical working capacity was unchanged. An incidence of 4.5 per cent of pericarditis in a large series of patients has been reported (STEWART & FAJARDO 1971) but the onset was delayed for more than a year in many cases. The true incidence of pericardial effusion in the present material is not known and echocardiography, the method of choice, was not available in the hospital at the time of the investigation.

In conclusion, a high incidence of ECG T-wave changes following left-sided irradiation for breast carcinoma was noted, but the perimyocardial damage indicated by these ECG changes was functionally insignificant in the short term and the incidence of serious cardiac complications was low.

SUMMARY

Cardiovascular complications from irradiation for breast carcinoma were assessed by history, physical examination, ECG recording, exercise test and heart volume determination before and two and six months after treatment in 197 unselected patients. A deterioration in general condition during therapy was reported by about 50 per cent of the patients, with shortness of breath and palpitation of the heart as the most frequent complaints and with a gradual improvement after therapy. Clinically, one case of pericarditis was diagnosed. ECG T-wave abnormalities appeared in 35 per cent of the patients after treatment, essentially confined to patients with left-sided pre- or postoperative treatment, where the mean radiation dose to the anterior quarter of the heart usually exceeded 20 Gy. Physical working capacity two and six months after therapy did not seem to be influenced by irradiation alone, and no correlation existed between change in physical working capacity and appearance of ECG T-wave abnormalities. The heart volume increased by more than 200 ml in 2 patients but otherwise the changes in heart volume were small. A high incidence of ECG T-wave abnormalities following left-sided irradiation for breast carcinoma was noted, but in the short term these ECG changes were functionally insignificant.

REFERENCES

ADOLFSSON G.: Circulatory and respiratory function in relation to physical activity in female patients before and after cholecystectomy. Acta chir. scand. (1969) Suppl. No. 401.

ÅSTRAND I., ARESKOG N.-H., CARLSTEN A., GREWIN K.-E., KAIJSER L., MALMSTRÖM G., PUNSAR S., BLOMQVIST G., BJERKELUND C., FURBERG C., HANSEN F., KALLIO V., NORDGREN L., PYÖRÄLÄ K. and THULESIUS O.: The 'Minnesota code' for ECG classification. Adaptation to CR leads and modification of the code for ECGs recorded during and after exercise. Acta med. scand. (1967) Suppl. No. 481.

ATTERHÖG J.-H. and MALMBERG P.: Prevalence of primary T-wave changes in young men and their relationship to psychological and anthropometric data. Clin. Cardiol. 4 (1981), 91.

BIRAN S., HOCHMANN A. and STERN S.: Therapeutic irradiation of the chest and electrocardiographic changes. Clin. Radiol. 20 (1969), 433.

CATTERALL M. and EVANS W.: Myocardial injury from therapeutic irradiation. Brit. Heart J. 22 (1960), 168.

COHN K. E., STEWART J. R., FAJARDO L. F. and HANCOCK E. W.: Heart disease following radiation. Medicine 46 (1967), 281.

COOPER E. E.: Breast cancer. Radiation effects on the myocardium. Tex. Med. 63 (1967), 52.

DEEDS D. and BARNES A. R.: Characteristics of chest lead electrocardiograms of 100 normal adults. Amer. Heart J. 20 (1940), 261.

FRANZÉN S. and ZAJICEK J.: Aspiration biopsy in diagnosis of the breast. Critical review of 3479 consecutive biopsies. Acta radiol. Ther. Phys. Biol. 7 (1968), 241.

GROSS N. J.: Pulmonary effects of radiation therapy. Ann. intern. Med. 86 (1977), 81.

JONES A. and WEDGWOOD J.: Effects of radiations on the heart. Brit. J. Radiol. 33 (1960), 138.

JONSSON B. and ÅSTRAND I.: Electrocardiographic findings in men and women aged 18 to 65. Scand. J. soc. Med. 5 (1977), 41.

KJELLBERG S. R., LÖNROTH H. and RUDHE U.: The effect of various factors on the roentgenological determination of the cardiac volume. Acta radiol. 35 (1951), 413.

LAMONTE C. S. and FREIMAN A. H.: The electrocardiogram after mastectomy. Circulation 32 (1965), 746.

LEACH J. E.: Effect of roentgen therapy on the heart. Arch. intern. Med. 72 (1943), 715.

ROSE G. A. and BLACKBURN H.: Classification of the electrocardiogram for population studies. *In*: Cardiovascular survey methods, p. 137. WHO monograph series No. 56. WHO, Geneva 1968.

RUBIN P. and CASARETT G. W.: Clinical radiation pathology, p. 471. W. B. Saunders Company, Philadelphia 1968.

SJÖSTRAND T.: Functional capacity and exercise tolerance in patients with impaired cardiovascular function. *In*: Clinical cardiopulmonary physiology, p. 201. Grune and Stratton, New York 1960.

SNEDECOR G. W. and COCHRAN W. G.: Statistical methods. Sixth edition. The Iowa State University Press, Ames, Iowa, USA 1967.

STEWART J. R. and FAJARDO L. F.: Radiation-induced heart disease. Clinical and experimental aspects. Radiol. Clin. N. Amer. 9 (1971), 511.

WHITFIELD A. G. W. and KUNKLER P. B.: Radiation reactions in the heart. Brit. Heart J. 19 (1957), 53.