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INCIDENCE OF INFECTIOUS SYMPTOMS AFTER RADIATION THERAPY FOR BREAST CANCER

Long-term effects

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Abstract

The incidence of symptoms generally associated with infectious disease was assessed by a questionnaire sent out to 519 disease-free breast cancer patients 7 to 12 years after primary treatment. All patients were treated in the context of a randomized trial where pre- and postoperative radiation (45 Gy) was evaluated versus surgery only. The results indicate a significantly higher morbidity among patients treated with preoperative irradiation compared with those irradiated postoperatively ($p < 0.05$). This increased morbidity mainly seemed to be caused by symptoms usually associated with respiratory tract infection ($p < 0.05$). Although statistically not significant the preoperatively irradiated patients also had a higher morbidity than those treated with surgery alone. There was no difference between postoperatively irradiated patients and patients treated with surgery only. A significantly higher integral dose (absorbed energy within the body) of the pre- compared with the postoperative group ($p < 0.025$) is associated with the differences in morbidity between the two irradiated groups. An explanation for the increased morbidity seems to be that the volume of lung tissue, encompassed within the full-dose target volume, is the crucial factor. This volume was considerable in the preoperatively treated patients but kept at a minimum in the postoperative group.

Key words: Radiations, injurious effects; breast cancer, postoperative irradiation, infectious symptoms, long-term effects.

Local radiation therapy as an adjunct to surgery is widely used in the management of breast cancer. Its beneficial effect in controlling local and regional disease is well documented. However, a beneficial effect on survival has so far not been convincingly proven (3, 5–8, 11, 13, 25), though some studies have indicated such a possibility (6, 25).

The randomized trial in progress at Radiumhemmet from 1971 and through 1976 was initiated to determine the clinical value of pre- or postoperative radiation compared with surgery only in breast cancer patients. After an initial significant increase in survival among preoperatively irradiated patients (24, 25), the latest survival analysis performed after a follow-up of 8 to 14 years (mean 11 years) failed to detect significant differences in survival between the various treatment groups (26).

In a recent series of articles we presented evidence for long-term changes of the composition and function of the blood lymphocyte population in irradiated breast patients participating in the above mentioned trial (15–18). Since the clinical relevance of these changes is unknown, we considered it of importance to investigate whether the irradiated women have an increased incidence of infectious symptoms several years after treatment.

Material and Methods

The patients entered a randomized trial during the years 1971 to 1976 to determine the clinical effect of pre- or postoperative irradiation compared with surgery only in operable breast cancer. Seven to 12 years after completion of initial therapy, 519 of the 960 patients included in the trial had no evidence of disease. These patients were chosen as our study group. One hundred and seventy-nine of these patients had received preoperative radiation, 181

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patients postoperative radiation and 159 had been treated with surgery only. The patients were aged 35 to 81 years and the mean age in the three treatment groups was 66, 64 and 66 years, respectively. The lower numbers of patients treated with surgery only was due to an increase in recurrence-free survival among irradiated patients (25).

Therapy. Modified radical mastectomy was the surgical procedure for all patients (24, 25). Details of the radiation therapy techniques have been described before (21). In short, the target volume for radiation therapy (45 Gy) included the breast or chest wall and lymph nodes in the axilla, the supraclavicular, the internal mammary regions. The affected breast and internal mammary nodes were included in the same target volume by ^{60}Co beams. Postoperatively an oblique electron beam was used to treat the chest wall and internal mammary nodes. In both irradiated groups, the axilla and supraclavicular areas were treated by ^{60}Co fields. During the first two years of the trial the internal mammary nodes of both sides were treated (wide field technique) and thereafter only the ipsilateral one (limited field technique). Among the patients included in this presentation, 119 out of 360 irradiated patients received treatment according to the wide field technique. These included 62 patients irradiated preoperatively and 57 treated postoperatively. The corresponding number in the limited field group was 117 and 124, respectively.

Calculation of integral dose. A sample of 40 dose plans obtained from patients treated with wide and limited field techniques from pre- and postoperatively irradiated patients (10 patients in each treatment group) was randomly chosen for calculation of integral doses. The integral doses, defined originally by MAYNEORD (9) as the absorbed energy in the body from ionizing radiation and measured in joule (J), were calculated as the product of the mean absorbed dose to the different tissues and the masses of the tissues. The lung density was assumed to be 0.25 g/cm^3 according to VAN DYKE et coll. (23). It was further assumed that the dose was zero outside the cranial and caudal limits of the fields. The height of the field was assumed to be 15 cm for all patients.

The treatments have been given according to individual dose plans made in one cross section in the middle of the field height. This cross section was assumed to be representative throughout the field height. The mean absorbed dose and the volume at the different tissues were calculated by a computerized dose planning system.

Questionnaire. The incidence of symptoms generally associated with infectious disease was assessed by patients using a daily record card. In addition patients were asked about the number of days being absent from work or being confined to bed. Recorded symptoms are presented in Table 1. During February, March and April 1983 questionnaires were mailed to all 519 disease-free patients.

Data processing and statistical calculation. The information derived from the questionnaires was computerized

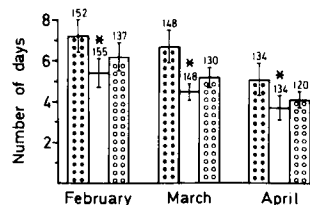


Fig. 1. Number of days during which the patients experienced at least one symptom as assessed by a questionnaire. Mean \pm SE are presented. Preoperative irradiation (□), postoperative irradiation (◻), surgery only (◼). Asterisks indicate differences between pre- and postoperatively irradiated patients ($p < 0.05$). Figures above the bars indicate number of patients completing the questionnaire.

Table 1

Number of days with symptoms per month of each patient as assessed by a questionnaire. Mean \pm SE are presented; p -values denote the statistical significance of difference between pre- and postoperatively irradiated patients

	Preoperative group (n=155)	Postoperative group (n=155)	Surgery group (n=138)
1) Coryza	2.6 \pm 0.5	1.7 \pm 0.3	1.6 \pm 0.3
2) Cough	1.7 \pm 0.4	1.3 \pm 0.3	1.4 \pm 0.4
3) Fever	0.5 \pm 0.1	0.5 \pm 0.1	0.5 \pm 0.2
4) Sore throat	0.8 \pm 0.2	0.6 \pm 0.2	0.6 \pm 0.1
5) Watery eyes	1.6 \pm 0.4	0.7 \pm 0.3	0.6 \pm 0.3
6) Headache	1.2 \pm 0.3	0.9 \pm 0.2	0.9 \pm 0.3
7) Myalgia	2.7 \pm 0.6	1.5 \pm 0.7	2.0 \pm 0.5
8) Cold sores	0.5 \pm 0.2	0.3 \pm 0.1	0.3 \pm 0.2
9) Shingles	0.1 \pm 0.1	0.1 \pm 0.1	0.2 \pm 0.2
10) Nausea	0.3 \pm 0.1	0.1 \pm 0.1	0.2 \pm 0.1
11) Vomiting	0.03 \pm 0.02	0.02 \pm 0.02	0.05 \pm 0.03
12) Diarrhea	0.3 \pm 0.2	0.1 \pm 0.1	0.2 \pm 0.1
Any of the symptoms above	6.4 \pm 0.7	4.5 \pm 0.6	5.1 \pm 0.7

$p < 0.05$

for data processing by a person without knowledge of the codes representing the different treatment groups. The morbidity differences between the treatment groups were assessed by recording the number of days with at least one of the symptoms asked for in the questionnaire. Differences of means between groups were tested using the Student's t -test.

Results

A total of 1557 questionnaires were dispatched to the 519 patients. At completion of the study, 82 per cent had been returned. There was a slight decrease in patient numbers during the last month of the study but as can be seen from Figs 1 and 2 the frequency of patients completing the questionnaires was similar in all treatment groups.

Table 1 shows that symptoms usually associated with respiratory tract infections were the most common com-

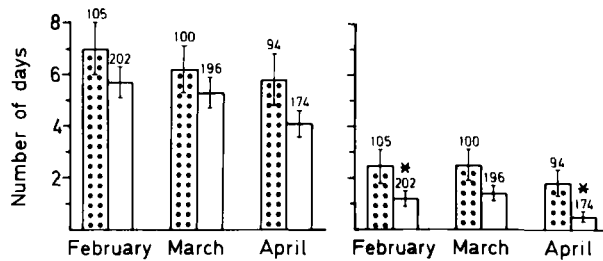


Fig. 2. Number of days during which the patients experienced at least one of the 12 symptoms (left) or only the symptom of cough (right) as assessed by a questionnaire. Mean \pm SE are presented. Patients treated with field technique (\square), patients treated with limited field technique (\square). Asterisks indicate differences between patients receiving wide and limited field irradiation ($p < 0.05$). Figures above the bars indicate number of patients completing the questionnaire.

Table 2

Total radiation energy absorbed in the body and numbers of symptom giving days per month as assessed by the questionnaire. *p*-values denote the statistical significance of differences between patients irradiated with wide and limited field techniques. Mean \pm SE are presented

	Wide field technique		Limited field technique
Total energy absorbed (J)	96.0 \pm 4.7	$p < 0.025$	69.0 \pm 5.2
	n=20		n=20
Total energy absorbed to the ipsilateral lung (J)	10.1 \pm 0.4	$p < 0.001$	7.6 \pm 1.8
	n=20		n=20
Total energy absorbed to the contralateral lung (J)	2.4 \pm 0.4	$p < 0.001$	0.8 \pm 0.2
	n=20		n=20
Symptoms (1-12)	6.4 \pm 0.9	NS	4.9 \pm 0.6
	n=105		n=205
Symptoms (2)	2.2 \pm 0.5	$p < 0.05$	1.0 \pm 0.2
	n=105		n=205

plaint of the patients. No single symptom differed significantly between the three treatment groups. However, Table 1 and Fig. 1 show that the mean number of days per month during which a patient experienced any of the 12 recorded symptoms was significantly higher in the preoperatively irradiated patients compared with those irradiated postoperatively. As the number of days usually associated with respiratory tract infections (symptoms 1-8) dominated in all three treatment groups differences in morbidity patterns were almost entirely confined to these symptoms ($p < 0.05$). The morbidity of preoperatively irradiated patients was also higher than that of patients treated with surgery only. This difference, however, was not statistically significant. The postoperatively irradiated patients did not differ from those who had undergone surgery only. There was no difference between the groups of

patients with respect to number of days being absent from work or confined to bed (data not shown).

In order to understand the differences between pre- and postoperatively irradiated patients the integral doses were calculated in 20 patients from each group. The integral doses were significantly higher ($p < 0.025$) in the preoperatively irradiated patients (92.4 ± 6.6) than in the postoperatively irradiated group (72.6 ± 4.5).

To further study the possible relation between integral dose and incidence of infectious symptoms, the above patients were divided into those who had been treated with wide field and limited field techniques. Table 2 shows that the mean integral dose was significantly higher in patients treated with wide field technique. Significantly higher amounts of absorbed energy were also noted in both lungs of these patients. When morbidity was compared between these two treatment groups a trend towards an increased number of days with monthly symptoms was noted in the patients who were irradiated with wide fields (Table 2, Fig. 2). The differences between the two groups mainly seem to be due to the symptom of cough.

Discussion

In the Scandinavian countries the late winter months are usually the time of intensive outbreaks of various viral diseases. Consequently February, March and April were chosen as suitable months to evaluate if adjuvant radiation therapy for breast cancer increases the susceptibility to infections. The results of the present study, on patients treated 7 to 12 years earlier, indicate that patients who had received preoperative radiation therapy experienced symptoms during more days per month than those who received postoperative irradiation during the same time period ($p < 0.05$) (Table 1, Fig. 1). However, there were no significant differences between patients who received postoperative irradiation and those who had been treated with surgery only.

The mechanism by which radiation therapy may increase susceptibility to infections is not known. Radiation induced changes of the lung parenchyma may increase susceptibility to local infections or produce symptoms which mimic a respiratory tract infection (2, 10, 12, 14, 20). Radiation therapy may also reduce the resistance of the mucosa of the respiratory tract (1, 4) thus facilitating the invasion of microorganisms. These changes seem to be strongly related to the irradiated lung volume (14). In both irradiated patient groups the same dose was given to the tumor volume. The postoperative patients were, however, irradiated with electron energies adjusted to cover the full-dose target volume area of the chest-wall, with a minimum dose to the lung tissue (21). In the preoperative group, where tangential photon beams were given a markedly higher volume of lung tissue was treated with full-dose (target dose) compared with the postoperatively

irradiated patients (21). At present we believe that this difference may explain the increased morbidity among the preoperatively irradiated patients. This is further supported by the relative steepness of the sigmoid dose-response curve for radiation induced pneumonitis (19, 22). If the dose-response curve is of similar shape for the effects studied here only the volume that receives a relatively high absorbed dose is relevant for the observed clinical effect.

It is also possible that the radiation induced impairment of the patients general immune response, which has been demonstrated to be rather long-standing, has contributed to the increased morbidity in infectious-like symptoms. This impairment is somewhat more marked in the preoperative group (15, 17) and could possibly be related to the total radiation energy absorbed (Table 2). It was also observed that patients treated with wide field technique had higher morbidity than patients treated with limited field technique (Table 2, Fig. 2). The trends were the same when patients were divided into pre- and postoperatively irradiated patients. The problem of increased infectious symptoms could also be due to an impairment of interferon production in irradiated patients thus rendering them more susceptible to viral infections. Theoretically, this impairment could be related to the total absorbed radiation energy (integral dose).

The approximations made in the integral dose calculations were depending on the limitations in anatomic data available for each patient. This may result in different systematic errors in the calculated integral doses for the pre- and postoperative treatment. It is, however, not probable that the significant difference in integral dose between the two groups is affected by this error. The higher integral dose in the preoperatively irradiated group is simply due to a larger irradiated volume. In the comparison between the wide and limited field techniques (Table 2) the systematic error has the same magnitude for the two groups. Treatment to the axilla and supraclavicular fossa was performed in a similar way in both irradiated patient groups. The mean values of the integral doses to these volumes are thus expected to be the same in the two groups. However, as no dose plans were available for these volumes the individual integral doses to these sites were not calculated.

A common problem in studies such as the present is the phenomenon of recall bias. In our case it is unlikely that patients who were previously irradiated suspected long-term health hazards of this treatment since our questionnaires and letters to the patients did not contain any reference to a previously performed irradiation. In addition our target population was disease-free and mostly symptom-free for a relatively long period of time thus minimizing the effect of recall bias.

In *conclusion*, the present results suggest that preoperative adjuvant radiation therapy in our breast cancer patients examined 7–12 years after treatment might have

increased their sensitivity to infections, aggravated or mimicked such symptoms. Such a finding might be of importance considering an increased acceptance of breast preserving surgery with local radiation therapy. The difference between irradiated and non-irradiated patients, however, was relatively small and therefore it is unlikely that this morbidity markedly impairs the quality of life of these patients. It should also be stressed that the dominance of subjective and sometimes unspecific symptoms in our questionnaire makes it difficult to draw general conclusions on long-term effects on the health status of irradiated breast cancer patients. Further studies to elucidate this important question are warranted.

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REFERENCES

1. CHU F. C. H., PHILLIPS R., NICKSON J. J. and MCPHEE J. G.: Pneumonitis following radiation therapy of cancer of the breast by tangential technic. *Radiology* 64 (1955), 642.
2. FERGUSON D., SUTTON JR H. and DAWSON P.: Late effects of adjuvant radiotherapy for breast cancer. *Cancer* 54 (1984), 2319.
3. FISCHER B., SLACK N. H., CAVANAUGH P. J., GARDENER G. and RAVDIN R. G.: Postoperative radiotherapy in the treatment of breast cancer. Results of the NSABP clinical trial. *Ann. Surg.* 172 (1970), 711.
4. GROSS N. J.: Pulmonary effects of radiation therapy. *Ann. Intern. Med.* 86 (1977), 81.
5. HAMILTON T., LANGLANDS A. O. and PRESCOTT R. J.: The treatment of operable cancer of the breast. A clinical trial in the South-East Region of Scotland. *Brit. J. Surg.* 61 (1974), 758.
6. HØST H. and BRENNHOVD L. O.: The effect of postoperative radiotherapy in breast cancer. *Int. J. Radiat. Oncol. Biol. Phys.* 2 (1977), 1061.
7. KAAE E. and JOHANSEN H.: Simple mastectomy plus postoperative irradiation by the method of McWhirter for mammary carcinoma. *Ann. Surg.* 6 (1969), 895.
8. MCWHIRTER R.: The value of simple mastectomy and radiotherapy in the treatment of cancer of the breast. *Brit. J. Radiol.* 21 (1978), 599.
9. MAYNEORD W.: The measurement of radiation for medical purposes. *Proc. Phys. Soc.* 54 (1942), 405.
10. MÖBIUS W., MÜLS W. und STOLF W.: Einseitige Lungenparenchymerkrankung (Zytomegalieinfektion) nach postoperativer Bestrahlung eines Mammakarzinoms. (Fallbericht.) *Prax. Klin. Pneumol.* 37 (1983), 34.
11. PATERSON R. and RUSSEL M. H.: Clinical trials in malignant disease. Part III. Breast cancer. Evaluation of postoperative radiotherapy. *J. Fac. Radiol. (London)* 10 (1959), 175.
12. POLANSKY S., RAVIN C. and PROSNITZ L.: Pulmonary changes after primary irradiation for early breast carcinoma. *Amer. J. Roentgenol.* 134 (1980), 101.
13. ROBBINS G. C., LUCAS J. C., FRACCHIA A. A., FARROW J. H. and CHUS F. CH. H.: An evaluation of postoperative prophylaxis.

- lactic radiation therapy in breast cancer. *Surg. Gynecol. Obstet.* 122 (1966), 979.
14. ROTHWELL R. I., KELLY S. A. and JOSLIN C. A. F.: Radiation pneumonitis in patients treated for breast cancer. *Radiother. and Oncol.* 4 (1985), 9.
 15. ROTSTEIN S., BLOMGREN H., PETRINI B., WASSERMAN J. and BARAL E.: Long term effects on the immune system following local radiation therapy for breast cancer. I. Cellular composition of the peripheral blood lymphocytes population. *Int. J. Radiat. Oncol. Biol. Phys.* 11 (1985), 921.
 16. — — — — — Long term effects on the immune system following local radiation therapy for breast cancer. III. Changes of spontaneous and lectin dependent cellular cytotoxicity. *Anticancer Res.* 6 (1986), 113.
 17. — — — — — Long term effects on the immune system following local radiation therapy for breast cancer. IV. Proliferative responses and induction of suppressor activity of the blood lymphocyte population. *Radiother. Oncol.* 6 (1986), 223.
 18. — — — — — von STEDINGK L.-V., PETRINI B., WASSERMAN J. and BARAL E.: Long term effects on the immune system following local irradiation for breast cancer. II. Poke weed mitogen induced immunoglobulin secretion by blood lymphocytes and serum immunoglobulin levels. *Eur. J. Surg. Oncol.* 11 (1985), 137.
 19. RUBIN P.: The Franz Buschke lecture: Late effects of chemotherapy and radiation therapy. A new hypothesis. *Int. J. Radiat. Oncol. Biol. Phys.* 10 (1984), 5.
 20. — — and CASARETT G.: Respiratory system. *In: Clinical radiation pathology*, p. 423. W. B. Saunders, Philadelphia 1968.
 21. STRENDER L.-E., WALLGREN A., ARNDT J. et coll.: Adjuvant radiotherapy in operable breast cancer. Correlation between dose in internal mammary nodes and prognosis. *Int. J. Radiat. Oncol.* 7 (1981), 1319.
 22. VAN DYKE J., KEANE T. J., KAN S., RIDER W. D. and FRYER C. J. H.: Radiation pneumonitis following large single dose irradiation. A re-evaluation based on absolute dose to the lung. *Int. J. Radiat. Oncol. Biol. Phys.* 7 (1981), 461.
 23. — — and RIDER W. D.: Lung density as measured by computerized tomography. Implications for radiotherapy. *Int. J. Radiat. Oncol. Biol. Phys.* 8 (1982), 1363.
 24. WALLGREN A., ARNER O., BERGSTRÖM J. et coll.: Preoperative radiotherapy in operable breast cancer. Results of the Stockholm cancer trial. *Cancer* 42 (1978), 1120.
 25. — — — — et coll.: The value of preoperative radiotherapy in operable mammary carcinoma. *Int. J. Radiat. Oncol. Biol. Phys.* 6 (1980), 287.
 26. — — — — et coll.: Radiation therapy in operable breast cancer. Results from the Stockholm trial on adjuvant radiotherapy. *Int. J. Radiat. Oncol.* 12 (1986), 553.