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DECREASED SURVIVAL RELATED TO IRRADIATION POSTOPERATIVELY IN EARLY OPERABLE BREAST CANCER

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Summary An increased mortality in early breast cancer can be correlated to the routine use of local postoperative irradiation. The decreased survival is statistically significant. Of controlled clinical trials so far published, all six, including more than 3400 patients, demonstrate decreased survival of between 1 and 10% in irradiated patients when compared with those treated by mastectomy alone.

CARCINOMA of the breast is in many countries the most frequent tumour in women.¹ Cure-rates have been improving, mainly due to earlier detection,² but when patients at the same clinical stage are compared, survival-times have not changed much over the past 30 years despite great technical improvements in treatment methods. This may be because breast cancer is so often a disseminated disease at time of diagnosis. Despite our classification of the tumour as localised (e.g., $T_{1/2}N_{1/0(+)}M_0$ on the TNM system) about 50% of patients die within 5 years with distant metastases.

Now that such attention is being paid to the allocation of medical resources, the routine use of doubtful treatment methods must be questioned—especially if the treatment can be shown to be positively harmful to the patient. The routine use of postoperative radiotherapy may be such a treatment method. The positive effect³⁻⁷—namely, the lower risk of local and regional recurrences—is proven, and for most clinicians this has been motivation enough for adopting the method. However, most of us agree that increased survival is the main priority, and in breast cancer distant metastases are the most serious problem. Local

irradiation does not lead to increased survival, and most trials end by saying that no statistical difference could be found between the two treatments being compared (e.g., operation alone or operation plus postoperative irradiation). Some end by saying that further studies are needed or that late survival data must be awaited before analysing the results. It may not necessarily be so.

In six controlled trials³⁻⁸ the effect of preoperative or postoperative radiotherapy can be evaluated. In all, survival-rates were lower in the irradiated group: the increased mortality in the irradiated groups varies between 1% and 10% 5 years after treatment (table I).

Leaving aside the Berlin trial,⁸ in which the irradiation was preoperative, the remaining five trials had relatively comparable treatments. One can combine the 5-year-survival results of these five trials by the Mantel-Haenzel procedure.⁹ This procedure gives a

TABLE II—INCREASED MORTALITY AFTER POSTOPERATIVE IRRADIATION IN BREAST-CANCER PATIENTS AS COMPARED WITH OPERATION ONLY IN RELATION TO AGE OR MENSTRUAL STATUS

	Increased mortality (%)
Manchester (5 yr.)	
Age ≤ 45	+14
Age > 65	-2
N.S.A.B.P. (3 yr.) N+	
Premenopausal	+16
Postmenopausal	+3

N+ = Patients with lymph-nodes positive for tumour.

chi-squared value on one degree of freedom of 4.22, giving a significance level of $P=0.04$. Two reservations are needed, first that only the five-year survival has been considered, rather than the complete survival curve. However, general experience of breast cancer suggests that trends established at five years continue,¹⁰ and before five years one might expect a greater proportional difference if immunosuppression is a relevant factor. Secondly, aspects of the design of each trial such as stratification may modulate the crude use of the Mantel-Haenzel procedure, but one would expect greater rather than less significance if account was taken of stratification in the analysis, with the identification of high-risk groups (e.g., table II).

Postoperative irradiation may not affect all patients

TABLE I—DECREASED SURVIVAL CORRELATED TO IRRADIATION POSTOPERATIVELY IN "EARLY" OPERABLE BREAST CANCER AS INDICATED BY ALL RANDOMISED TRIALS PUBLISHED

Study/Ref.	Years postop.	Survival-rate (%)		Living at start of interval:		Remarks	Increased mortality in irradiated groups (%)
		Surgery + irradiation	Surgery only	Surgery + irradiation	Surgery only		
Manchester ^{3,4,14} O	5	55	56.5	327	393	Postop. irradiation by "quadrant" technique after radical mastectomy	1.5
	7	45.4	48				2.6
	10	42.7	44				1.3
Manchester ^{3,4,14} P	5	56.5	61	382	359	Postop. irradiation by "peripheral" technique	4.5
	7	49	51				2
	10	44.2	47.5				3.3
Copenhagen ⁴	5	66	67	219	206	Super radical compared with simple mast. + postop. stage I, II (III)	1
	5	66	67				
Edinburgh ⁴	1	93.8	96.7	191	204	Radical mastectomy compared with simple + postop. irradiation stage I, II (III). All castrated by irradiation too	2.9
	5	66	76	109	94		10
N.S.A.B.P. 1970 ⁷	3	70	77	470	317	Radical mastectomy compared with radical mastectomy postop. radiotherapy	7
	4	61	69				8
	5	56	62				6

Comparing surgery only against surgery + irradiation by the Mantel-Haenzel procedure⁹ gives $\chi^2 = 4.22$ ($P = 0.04$).

Preoperative irradiation before radical mastectomy as compared to radical mastectomy only was related to an increased mortality of +5% at 3 years and +7% at 5 years after operation in a controlled series of 82 and 72 patients per group.⁸

negatively. Can some patients be defined whose survival specifically is affected by irradiation? The importance of well-stratified clinical trials and the danger of generalisations is indicated by table II. In fact, when separating patients according to age and comparing the effect of added radiotherapy after mastectomy, the two studies^{3,7} in which the data published allow this analysis indicate that the negative effect of irradiation on survival may be correlated to age or hormonal status. An increased mortality of 14-16% after irradiation can be found in the younger fertile women while the older non-fertile women seem to be saved from the negative effect. However, were the women routinely castrated by irradiation, such an age-correlated difference was not seen in another of the controlled studies.⁶

A possible explanation for the increased mortality in the irradiated groups may be the effect of irradiation on host immunity. In a situation where we have minimal residual tumour cells, later expressing themselves as metastases, local irradiation leads to a long-

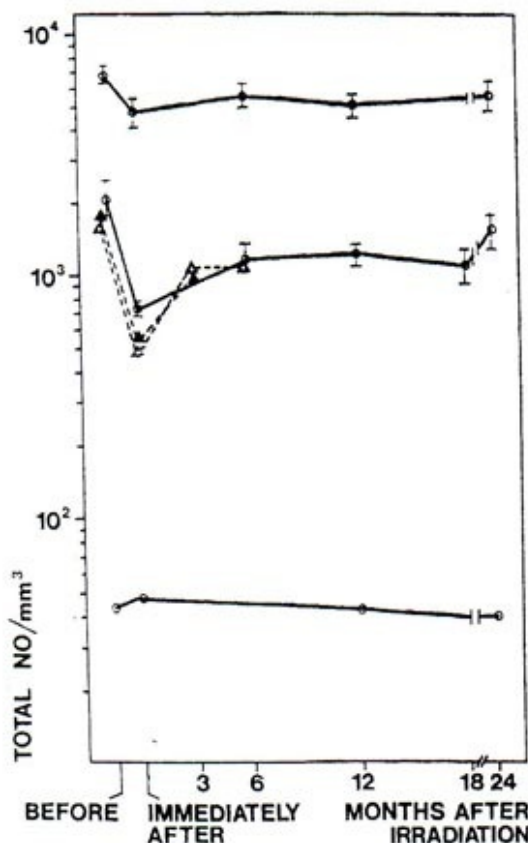
lasting lymphopenia (see figure). Tumour-associated immune reactions against human breast cancer have been found in vivo and in vitro, and it is possible that breast-cancer cells possess tumour-associated antigens that may induce rejection reactions of importance for the clinical outcome. The irradiation-induced decrease of host immunity in a situation where the patients have minimal residual tumour¹¹ may be related to the slight but constant earlier appearance or increase of distant metastasis.¹² This may give an indication of the importance, if any, of host anti-tumour immunity in a cancer patient where, by definition, early immune surveillance has already failed.

The routine use of postoperative irradiation in early breast cancer must be seriously questioned. Survival data argue against its use, despite the local effect on recurrence-rates. If the routine use of prophylactic local radiotherapy after radical mastectomy were stopped, survival might increase and resources might be saved. Only in centres where carefully controlled clinical analysis can be performed,¹³ leading to further understanding of the biology of breast cancer, can one justify the use of prophylactic radiotherapy in the search for new ways of its optimal application in early breast cancer.

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Effect of postoperative irradiation on total leucocyte, lymphocyte and monocyte counts.

The total no. of W.B.C. is significantly depressed up to 24 months in the 33 patients followed for this period. The counts before irradiation were 6770 ± 1617 , immediately after 4711 ± 1472 , and 24 months after 5537 ± 1469 (\pm s.d.).

A severe lymphopenia occurs immediately after irradiation, from $2065 - 692$ per c.mm. before irradiation to 745 ± 334 immediately afterwards. Even 1 or 2 years after irradiation a statistically significant lymphopenia was found— 1234 ± 263 and 1612 ± 542 per c.mm. (significant by *t* test at $P < 0.001$ and $P < 0.01$, respectively). For comparison, the lymphopenia observed after postoperative irradiation in two other clinics on 36 patients is plotted, demonstrating that it is not an isolated finding, counts being 503 ± 131 and 470 ± 192 lymphocytes per c.mm. before and immediately after irradiation, respectively.

No depressive effects were seen on the monocytes.

