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Post-mastectomy Megavoltage Radiotherapy: The Oslo and Stockholm Trials

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The ability of adjuvant radiotherapy to prevent distant metastasis and to prolong survival in patients with early breast cancer is much debated. The paper presents a joint analysis of long-term results (13–16 years' follow-up) from the Oslo and Stockholm randomised trials of post-operative megavoltage radiotherapy versus surgery alone. Among node-positive patients there was a significant 37% relative reduction of distant metastases with radiation ($P < 0.01$) and an overall survival difference in favor of the irradiated patients which corresponded with a 22% relative reduction of deaths of borderline significance ($P < 0.06$). No significant benefit with radiation in terms of distant metastasis-free survival or overall survival was observed among node-negative patients. The results show that effective local treatment can prevent distant dissemination in some patients and contradict the contention that node-positive breast cancer invariably is a systemic disease already at primary diagnosis.
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INTRODUCTION

THERE IS a general agreement that radiotherapy as an adjunct to surgery of early breast cancer prevents loco-regional recurrence and produces a sustained improvement of the disease-free interval [1–5]. On the other hand, the ability of radiation to prevent distant dissemination and to prolong overall survival is still much debated. Cuzick *et al.* [6], in their recent overview, concluded that post-operative radiotherapy has no effect on survival in the first 10 years of follow-up, but that it may have a significant deleterious effect after 10 years.

However, it has been suggested [7,8] that there is a subset of patients without subclinical distant metastases at the time of primary treatment that might benefit from radiotherapy in terms of survival. Among these patients, a complete loco-regional treatment [tumour excision, axillary dissection and irradiation of the internal mammary chain (IMC)] could prevent the development of distant metastases. This hypothesis goes against the idea that node positive breast cancer invariably is a systemic disease which can only be controlled by systemic therapy. Since histological positive lymph nodes of the IMC are more often found in patients with positive axillary lymph nodes (N+) and possibly in patients with tumours located in the inner part of the breast [9–11] this benefit should be most easily detected in N+ patients with medial tumours.

The present study was initiated to examine whether adjuvant megavoltage radiotherapy of the lymph nodes including the IMC might have a beneficial effect on survival and distant metastasis rates. This effect was to be evaluated in all patients and then more specifically according to the histological axillary involvement and the tumour location. To examine this hypothesis with as much power as possible, it was decided to analyse jointly data from the Oslo and Stockholm randomised trials of adjuvant megavoltage radiotherapy in patients treated by radical or modified radical mastectomy.

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METHODS

Selection of trials

The trials to be included had to satisfy the following criteria: (1) surgery consisting of mastectomy and axillary dissection (to ensure a complete loco-regional treatment); (2) randomisation between post-operative megavoltage irradiation of the regional lymph nodes (including the IMC) or no irradiation; (3) no chemotherapy had to be administered.

A search was made in the mentioned overview of radiotherapy trials [6]: only the Oslo-II and Stockholm-1 trials fulfilled these criteria. The excluded trials involved either simple mastectomy or orthovoltage irradiation. The Heidelberg trial—which included 143 patients—might have been included, but the data were not available at the time of this analysis. Moreover it has been criticised because of an imbalance in the number of patients in the treatment and control groups which suggests that the treatment allocation was not truly random.

Summarised description of trials

Oslo [3,12]. A total of 541 pre- and postmenopausal patients were included during 1968–1972. The surgery was a radical mastectomy. All patients were treated with a radiological castration. The patients were randomly allocated to surgery alone or to post-operative radiotherapy (cobalt-60). The target volume included the IMC, the supra- and infraclavicular regions and the apex of the axilla. The treatment was given with two anterior fields. The chest wall was not irradiated. The protocol dose was 50 Gy at 3 cm given with daily fractions of 2.5 Gy 5 days a week for a total treatment time of about 4 weeks. Protocol deviations occurred in less than 3% of the patients. Patients were seen 3–4 times a year for the first 2 years following treatment, then 2

Table 1. Comparison between Oslo and Stockholm patients

Characteristic	Centre: Oslo (%) (n = 541)	Centre: Stockholm (%) (n = 644)	P-value
Site			
Inner and central site	43	43	NS
Number of involved nodes			
0	66	63	
1	17	13	< 0.01
2+	17	24	
Clinical size (cm)			
< 2	19	17	
2–4.9	74	71	< 0.01
5+	7	12	
Age (years)			
25–45	19	14	
46–55	38	37	< 0.01
56+	42	48	

times a year for up to 5 years after treatment and once yearly thereafter.

Stockholm [5].

Between 1971 and 1976, 644 pre- and postmenopausal patients were randomly allocated to post-operative radiotherapy or to surgery alone. The randomisation was stratified by age, lymph node status and size of the tumour. The surgery was a modified radical mastectomy. The target volume included the chest wall, the IMC, the axilla, and the supra- and infraclavicular regions. Radiotherapy was given with high-voltage technique: cobalt-60 to the axilla and the supra- and infraclavicular regions, 10–15 MeV electrons to the chest wall. The protocol dose was 45 Gy with 1.8 Gy per fraction 5 days a week for a total treatment time of about 5 weeks. Protocol deviations occurred in less than 4% of the patients. Patients were followed-up every 3 months during the first 2 years, every 6 months 2–5 years after treatment, and yearly thereafter. The follow-up was by clinical examination alone. Chest X-rays, bone scans and blood tests were performed only if there were clinical signs or symptoms of possible relapse. Recurrent disease was generally established on the basis of histopathological and cytological examinations. However, the diagnosis of recurrence was sometimes established on unequivocal clinical or radiological data.

Patients' characteristics

The patients in the Oslo and Stockholm studies were followed, for this analysis, for an average of 16 and 13 years, respectively. 2 patients in Oslo (0.4%) and 1 in Stockholm (0.2%) were lost to follow-up because of emigration before the closing date of this study (January 1986). A total of 211 deaths and 142 metastases were observed in the Oslo trial and 263 deaths and 230 metastases in the Stockholm trial. Distant metastasis was defined as a recurrence outside the chest wall and target volume. This implied that a supraclavicular recurrence was recorded as a loco-regional—not distant—treatment failure.

Within each centre, randomisation ensured a balanced distribution of patient characteristics [3,12,5]. A comparison of the two studies is given in Table 1. Patients in the Stockholm study were significantly older, had larger tumours and were more frequently node-positive than patients in the Oslo study. These significant differences were also found in the subgroup of N+ patients. Moreover, among Stockholm N+ patients, inner and central tumours were significantly larger than lateral tumours ($P < 0.05$, the respective proportion of tumours < 2 cm, 2–5 cm and ≥ 5 cm were 13%, 64% and 23% for inner and central tumours, and 9%, 79% and 12% for lateral tumours).

Statistical methods

The effect of radiotherapy was measured by the relative risk of death or distant metastasis for the radiotherapy group versus the no radiotherapy group. Metastases were analysed with two measures: the metastasis-free rate and the metastasis-free survival rate. For the metastasis-free rate, the metastasis-free time is defined as the time from the date of randomisation to the date on which distant metastasis was detected or to the date of last follow-up; patients dying without evidence of distant metastasis were considered as free of metastasis at the date of death. A similar definition is used for the recurrence free rate. For the metastasis-free survival rate, an event is either a distant metastasis or a death and the metastasis-free survival time is the time from the date of randomisation to the date of the first of these events or to the date of last follow-up. Similarly for the disease free survival rate, an event is either a local regional recurrence, a distant metastasis or a death. The estimates, 95% two-sided confidence intervals (CI) and statistical tests were derived from multivariate Cox regression models [13,14], stratified by centre, fitted to the survival, metastasis-free, metastasis-free survival, recurrence free and disease free survival data. The Cox models contained all or part of the following variables categorised as in Table 1: treatment, tumour site, age, number of histologically involved lymph nodes, clinical tumour size and various interactions. The statistical significance of a variable or an interaction was based on a χ^2 test of twice the difference between the log-likelihood associated with a model including the variable and the log-likelihood of a model omitting the variable. Cox models with time dependent covariates were used to investigate the variation of the relative risk with time: either different treatment variables were defined before and after 10 years, either an additional treatment variable function of log-time was added in the model [14,15]. Computations were made with the BMDP software [15]. P-values larger than 0.10 are all denoted by NS (non significant).

RESULTS

Overall results

There was no significant (NS) difference in survival between the group of patients treated by post-operative radiotherapy and the group not treated by radiotherapy (Fig. 1a); the stratified relative risk (RR) of death for irradiated patients vs. non irradiated patients was 0.92 (CI: [0.77, 1.10]).

Figure 1b shows the distant metastasis-free rate of all patients by allocated treatment. There was a significant benefit with radiation ($P < 0.01$): the RR of distant metastasis for irradiated patients vs. non irradiated patients was 0.75 (CI: 0.61, 0.92). This risk was the same in Oslo and Stockholm: the χ^2 for heterogeneity was 0.01 (NS).

The effect of radiotherapy on distant metastasis-free survival was of borderline significance ($P < 0.06$; Fig. 1c), with a relative risk in favour of radiotherapy of 0.84 (CI: [0.71, 100]).

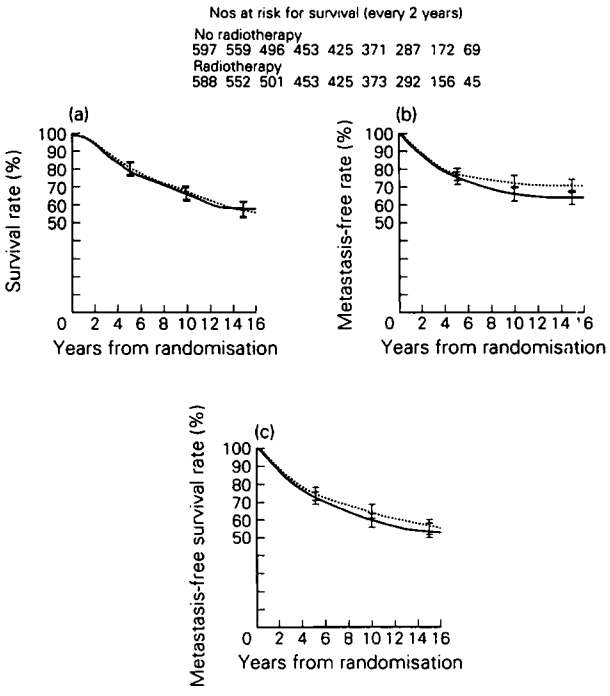

Fig. 1. (a) Survival rate, total population. (b) Distant metastasis-free rate, total population. (c) Distant metastasis-free survival rate, total population. ——— No radiotherapy; - - - - radiotherapy.

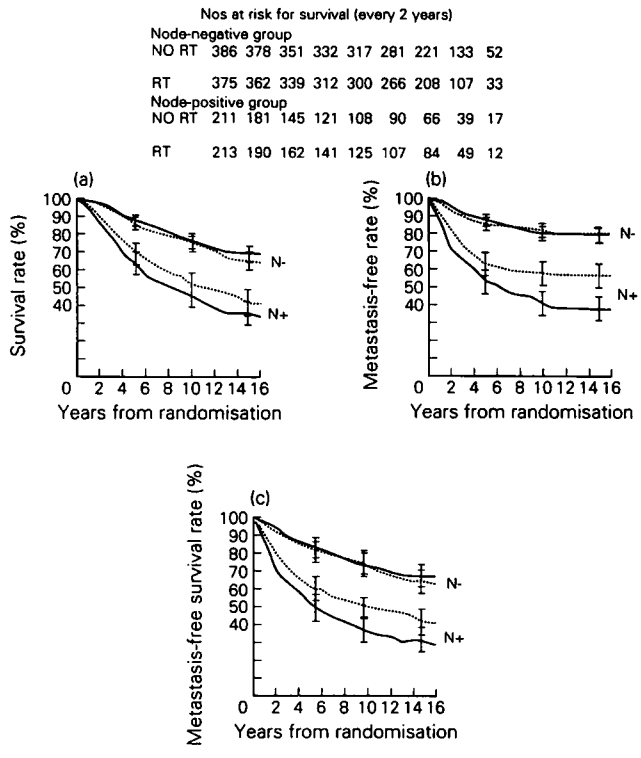

Fig. 2. (a) Survival rate, node-positive and node-negative patients. (b) Distant metastasis-free rate, node-positive and node-negative patients. (c) Distant metastasis-free survival rate, node-positive and node-negative patients. ——— No radiotherapy; - - - - radiotherapy.

Radiotherapy had a beneficial significant effect both on local regional recurrence ($P < 0.0001$) and disease free survival ($P < 0.001$), with respective relative risks of 0.27 (CI: [0.19, 0.38]) and 0.74 (CI: [0.63, 0.88]).

As mentioned in the statistical methods section, all the results were adjusted on the usual prognostic factors. As expected, tumour size and number of histologically involved lymph nodes were strong prognostic factors in all the analyses.

Results according to axillary node involvement

There was some evidence of interaction between treatment and lymph node status on the risk of distant metastasis ($\chi^2 = 4.05, P < 0.04$): the irradiated node-positive patients had a RR of distant metastasis of 0.63 (CI: [0.48, 0.83]) versus 0.97 (CI: [0.70, 1.33]) for the irradiated node-negative patients. Figure 2b shows the distant metastasis-free rate for the node-positive and node-negative patients. Again there was no indication of heterogeneity between the Oslo and Stockholm trials ($\chi^2 = 0.02$, NS) with approximately equal estimates of RR for the node-positives: 0.61 and 0.63, respectively.

Figure 2c shows the distant metastasis-free survival rate for the node-positive and node-negative patients. The interaction between lymph node status and treatment on the risk of death or distant metastasis was significant ($P < 0.02$): the relative risk among node-negative patients was 1.05 (CI: [0.82, 1.35]) versus 0.68 (CI: [0.53, 0.87]) among node-positive patients.

The interaction between treatment and lymph node status on the risk of death was weaker ($\chi^2 = 3.52$, $P < 0.10$). Among node-positive patients, there was a survival difference in favour of radiotherapy of borderline significance ($P < 0.06$; Fig. 2a) with a RR of death for irradiated patients vs. non irradiated patients of 0.78 (CI: [0.61, 1.00]). Among node-negative patients, there was no survival benefit with radiation: the RR of death was 1.10 (CI: [0.85, 1.43]).

The interaction between treatment and lymph node status on disease free survival was of borderline significance ($\chi^2 = 4.00$, $P < 0.05$). Among node-positive patients, the favourable effect of radiotherapy is highly significant ($P < 0.0001$) with a RR for irradiated patients vs. non irradiated patients of 0.61 (CI: [0.48, 0.78]). Among node-negative patients, the effect is NS with a RR of 0.88 (CI: [0.69, 1.12]).

There was no interaction between treatment and lymph node status on local regional recurrence.

Fig.3a,b show the estimated RRs of death and metastasis in the node-positive group according to the location of the tumour. The RRs for inner and central tumours were smaller than those for lateral tumours, but not significantly so (the χ^2 for interaction was 1.62, NS, for metastasis, 1.24, NS, for death and 2.35, NS, for metastasis or death). Therefore only the global estimate for all sites should be considered.

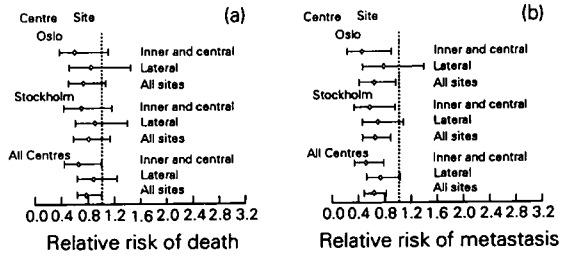

Fig. 3. (a) Relative risk of death for irradiated node-positive patients versus non irradiated node-positive patients by tumour location and treatment centre. (b) Relative risk of distant metastasis for irradiated node-positive patients versus non irradiated node-positive patients by tumour location and treatment centre.

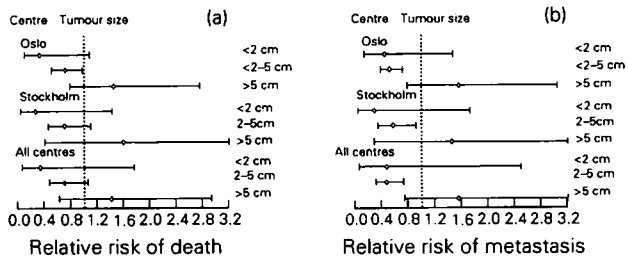

Fig. 4. (a) Relative risk of death for irradiated node-positive patients versus non irradiated node-positive patients by tumour size and treatment centre. (b) Relative risk of distant metastasis for irradiated node-positive patients versus non irradiated node-positive patients by tumour size and treatment centre.

The effect of radiation was significantly related to the size of the primary tumour. The test for trend indicated that the RR of distant metastasis was significantly lower for irradiated patients with small than with large tumours ($\chi^2 = 6.74$, $P < 0.01$, Fig. 4b). A similar trend was observed for the RR of death ($\chi^2 = 5.66$, $P < 0.02$, Fig. 4a).

Variation with time

Survival of more than 10 years was examined in all patients: 745 patients were alive at 10 years, and among them 81 deaths were observed after 10 years. The variation of RRs of death with time is presented in Table 2. There was no difference before and after 10 years globally or separately among node-positive and node-negative patients ($\chi^2 = 0.06$, NS). The test of linear variation of the relative risk of death with time was also non significant ($\chi^2 = 0.34$).

DISCUSSION

The present study showed a favourable effect of radiotherapy on the distant metastasis-free rate of node-positive patients ($P < 0.001$). A possible beneficial effect of radiation on survival corresponding to a 22% relative reduction of deaths ($P < 0.06$) in this group of patients should be interpreted with caution, since the overall effect was not significant.

Among node-positive patients, there was no statistical evidence that the effect of radiation on survival or metastasis rate was different for patients with inner and central tumours compared with those with lateral tumours, although the estimated differences went in the expected direction. On the other hand, the treatment effect was related to tumour size: the reduction of both distant metastasis and death was significantly greater among patients with small tumours.

Node-positive breast cancer has been described as a systemic disease already at primary diagnosis in most patients. According to this hypothesis, prevention of distant dissemination can only be achieved with systemic therapy. Our results do not seem to accord with this contention. Although the specific hypothesis of a larger effect for inner tumours in N+ patients, who have the highest rate of IMC involvement, was not supported by this study, possibly because of lack of power, the results are consistent with the biological assumption of multistep metastatic dissemination of breast cancer because the overall distant metastasis rate was significantly decreased in N+ patients treated by radiotherapy and there was a significant trend towards a larger effect of radiotherapy in N+ patients with small tumours for whom the risk of subclinical distant metastases should be lower. Koscielny *et al.* [16] have indeed shown that the mean tumour size at the time of distant dissemination is larger than the mean size at the time of first axillary nodal involvement.

Table 2. Variation of relative risk of death in time (all patients)

Centre	Time period		All years
	Years 0–9	Years 10+	
Oslo	0.97	1.13	1.00
Stockholm	0.87	0.75	0.86
All centres	0.91	0.97	0.92

Comparison of the relative risks in the two time periods: $\chi^2 = 0.06$, NS.

Could the difference in metastasis rates be explained by a detection bias? Metastases are perhaps diagnosed earlier among patients with a local recurrence because of increased diagnostic efforts following diagnosis of the relapse, and local recurrences were more frequent in the no radiotherapy group. However, a possible delay in the diagnosis of distant metastasis in the radiotherapy group probably did not exceed 2–3 years and most local recurrences (75%) occurred during the first 5 years. In contrast, the observed effect of radiation on distant metastases was most pronounced after 5 years: in node-positive patients, the RR of distant metastasis was 0.72 before 5 years compared with 0.31 after 5 years ($\chi^2 = 5.31$, $P < 0.03$). This possible bias is thus not sufficient to explain the observed difference in distant metastasis rate between the two groups.

The effect of radiation on survival among node-positive patients was less pronounced than on distant metastasis. A dilution of the treatment effect from an increasing number of intercurrent deaths during follow-up probably contributed to this observation. In addition, patients with distant metastases had a median survival time of 17 months after detection of their metastases and 15% of them survived more than 5 years. The effect of radiotherapy on survival might therefore be better evaluated after longer follow-up, although the problem of intercurrent deaths will tend to increase with time. An alternative could be to use "death from breast cancer" as the end-point, but such an analysis would introduce problems of ascertaining the cause-specific mortality.

The evaluation of radiotherapy can only be based on the joint study of metastases and deaths, since any lethal complication of the treatment would not appear in the sole comparison of metastasis rates. An analysis of metastases which is less specific but which incorporates this type of complication consists in studying metastasis-free survival, where the event is metastasis or death. Our results show that conclusions based on distant metastasis-free survival rates are very similar to those based on distant metastasis-free rates, except for the significance of the overall effect of radiotherapy.

The effect of radiotherapy on metastasis and on survival was similar in both centres, despite some differences in the therapeutic schedule (irradiation of the ovaries and no treatment of the chest wall in the Oslo trial). It should be pointed out that both trials permitted an unconfounded evaluation of the effect of radiotherapy, since all other treatments were systematically given to all patients included in the trials.

Our results are based on a joint analysis of only two studies. The criteria for the selection of trials were defined with the objective of assessing the role of a complete loco-regional treatment (tumour excision, axillary dissection and IMC radiotherapy) without chemotherapy and with adequate doses

of radiation (≥ 45 Gy) in relation to the histological nodal status. For that reason, trials including orthovoltage radiation or simple mastectomy were not included. The rationale was that radiotherapy—as surgery—is a local treatment method. Significant results can only be expected if the entire tumour and lymph node volumes are treated with adequate doses. The introduction of megavoltage radiation represented a major improvement in therapeutic radiology [17,18]. It permits the delivery of potentially tumoricidal doses of radiation to the entire target volume, which is difficult with orthovoltage techniques. In addition, simple mastectomy does not allow a histopathological staging. The agreement between clinical and histopathological nodal status is not good [9]. Therefore, an analysis by clinical nodal status might obscure treatment differences between node-positive and node-negative patients. None of the recent trials allow an evaluation of the effect of radiotherapy among patients not treated by chemotherapy or additive hormonotherapy [19].

The evaluation of radiotherapy by Cuzick *et al.* [6] included orthovoltage and megavoltage radiotherapy (77% of the patients come from trials using orthovoltage radiation), after radical or simple mastectomy. The present study should be regarded as an in depth analysis of two trials aimed at more specific questions. The specificity of our objective has to be balanced against the restricted sample size [20]. Other radiotherapy trials not satisfying our selection criteria may still be relevant to the present evaluation. Similar analyses of other radiotherapy trials should allow everybody to construct his own opinion depending on the degree of relevance attached to these trials.

In the overview by Cuzick *et al.* [6] there was no difference in survival between the radiotherapy and no radiotherapy groups in the first 10 years, but a detrimental effect of radiotherapy on survival after 10 years. Such a late effect of radiotherapy was not found here but, if this effect exists, the present study was not powerful enough to detect a shift of a comparable order of magnitude: only 81 deaths occurred after 10 years, whereas the Cuzick overview was based on 653 deaths after 10 years mostly from the older orthovoltage radiotherapy trials. Orthovoltage is no longer used and the evaluation of its effect has not much relevance for patient management in the 1980s. However long-term effects have also been associated with megavoltage treatment such as myocardial disease among node-negative patients in the Oslo trial [3]. It seems reasonable to assume that such effects are dependent on the given dose and dose distribution to the heart. Therefore it should be possible to prevent them by technical improvements (mixed ^{60}Co and electron beams to decrease the radiation dose to the mediastinum, for example) and by avoidance of large fraction sizes.

In summary, the significant long-term effect on distant metastases reported in this study indicate that complete local treatment can prevent distant dissemination in some node-positive breast cancer patients. Therefore, adequate megavoltage radiotherapy can play an important role in the primary management of these patients. The effect of loco-regional treatment in operable breast cancer certainly merits further investigation.

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