FROM THE GENERAL AND SURGICAL DEPARTMENTS, THE NORWEGIAN RADIUM HOSPITAL, MONTEBELLO, OSLO, NORWAY.

COMBINED SURGERY AND RADIATION THERAPY VERSUS SURGERY ALONE IN PRIMARY MAMMARY CARCINOMA

I. The effect of orthovoltage radiation

HERMAN HØST and IVAR O. BRENNHOVD

Although carcinoma of the breast is the most common malignancy in women, there is no general agreement as to the best treatment of an early case. This uncertainty relates not only to the type of surgery, but also to the value of radiation therapy as an adjunct to surgery. Figures have been published suggesting that radical mastectomy combined with postoperative irradiation produces the best treatment results (GUTTMANN 1967, HARRINGTON 1952, LEWISON & SMITH 1963, MARSHALL & HARE 1947, WATSON 1967). However, the results from Manchester (EASSON 1968) and from the National Surgical Adjuvant Project (FISCHER et coll. 1968) give little support to radiation therapy after radical mastectomy as it did not affect survival. Data from the latter reports even indicate that postoperative irradiation may increase the risk of and the rate of growth of distant metastases.

Radical mastectomy with axillary lymph node dissection and prophylactic postoperative irradiation has been widely used in the treatment of early carcinoma of the breast in Norway for many years. The present investigation, started a decade ago, was intended to evaluate postoperative irradiation as an adjuvant to surgery.

Submitted for publication 27 May 1974.

In Part I, which is presented here, a conventional roentgen therapy unit was used, and in Part II a ^{60}Co unit, with considerably increased dosage and altered treatment plan. The results from Part II are not yet available.

Material and Methods

Only women considered operable according to the criteria laid down by HAAGENSEN (1949) have been included in the material. Surgery, in principle, has been Halsted's standard radical mastectomy, consisting of an en bloc removal of the breast, pectoral muscles and axillary contents. The distinction between stages I and II was made on the basis of histology of the axillary nodes. Ovarian irradiation was also carried out as part of the primary treatment (NISSEN-MEYER 1965).

The trial was started in January 1964 and completed in December 1967. This report concerns 546 cases or about two-thirds of the total number of patients with carcinoma of the breast (stages I and II) admitted to the Norwegian Radium Hospital during this period. In its surgical department 383 patients were operated upon, while the remaining 163 patients had a radical mastectomy at another hospital.

Out of the patients with mammary carcinoma, stage I or II, admitted to the hospital during the period 263 were excluded for the following reasons: (1) A standard mastectomy of the Halsted type had not been performed, (2) the criteria for operability laid down by HAAGENSEN had not been followed, or (3) evidence of residual malignancy within the operation area existed.

The patients included in the trial were divided by randomization into two groups: (1) postoperative irradiation (irradiated group), and (2) no postoperative irradiation (control group).

Irradiation data were 200 kV with a half-value layer of 1.5 mm Cu. The internal mammary lymph node chain, the ipsilateral axilla, the supraclavicular fossa and the skin flaps were irradiated by two tangential opposing beams to the anterior chest wall with supporting beams to the supraclavicular fossa and the axilla.

The doses to the supraclavicular fossa and the axilla were respectively 3600 R and 1800 R, measured as skin dose. The tangential opposing fields were each irradiated with 2600 R, measured as free air dose in the centre of the beam. The actual dose to the skin of the chest wall was from 2500 R to 3100 R. Dose measurements performed on an Alderson phantom have revealed a rapid decrease of the dose in the depth. The latter is caused by absence of scatter as most of the beams from the tangential fields projects beyond the skin of the patient.

All patients have been followed up at close intervals for at least 5 years. If local recurrence or metastasis was detected, hormones, roentgen irradiation or both combined were given as indicated in the individual case.

Local recurrence was defined as reappearance of disease within the area of operation, which means the operation scar and the chest wall. Regional metastasis has been

defined as occurrence of the disease in the axilla or supraclavicular fossa, while distant metastasis has been defined as disease occurring elsewhere.

Results

The patients in stage I amounted to 345, of these 173 belonged to the irradiated group and 172 to the control group. Of 201 patients in stage II, 109 received postoperative irradiation, while 92 were allocated to the control group.

Survival rates according to the life table method have been calculated (Fig. 1). It will be observed that there is no difference between the irradiated group and the control group either in patients stage I or in those stage II. Five years after treatment 91.3 per cent of the irradiated patients in stage I were living, compared to 89.9 per cent of the control groups. In stage II the 5-year survival rates were 71.4 and 71.7 per cent, respectively.

The disease-free survival for patients stage I and stage II according to initial treatment appears in Fig. 2. No difference was found.

Although no differences have been demonstrated either in crude or in the disease-free survival, a comparison of the spread of the disease in the different treatment groups might be of interest.

Local recurrence has always been confirmed histologically except in cases with widespread distant disease at the same time. The rate of local recurrence in the two groups is given in Table 1. In stage I local recurrence was observed at the same rate in the irradiated patients as in the controls; whereas in patients with stage II disease local recurrence appears to be almost twice as frequent in the control group as in the irradiated group. This difference is, however, not statistically significant.

In the majority of cases the local recurrence appeared as part of widespread disease. In the remaining patients the local recurrence preceded later regional or distant metastases in 10 cases (8 controls and 2 irradiated patients), while in 6 patients (4 controls and 2 irradiated) further spread has not been observed.

Regional metastases to the axillary or supraclavicular nodes were mainly based on clinical examination. The frequency of regional spread appears in Tables 2 and 3. Homolateral axillary metastasis was observed in only 10 out of 546 patients (Table 2). Table 3 shows that postoperative irradiation reduced significantly the occurrence of later supraclavicular lymph node metastasis ($p < 1\%$) in patients in stage II. A similar but less evident trend is seen in cases in stage I.

Distant metastasis. The number of patients with distant metastasis and the time of appearance after primary treatment may be seen from Table 4. No difference existed between the two groups either in stage I or in stage II, and postoperative irradiation had no influence on the time when distant metastasis appeared in patients stage I. In patients stage II the data suggest that distant metastasis occurred earlier in the irradiated group than in the control group. It should be stressed, however, that 4 patients stage I in the control group had distant metastases within one year, while

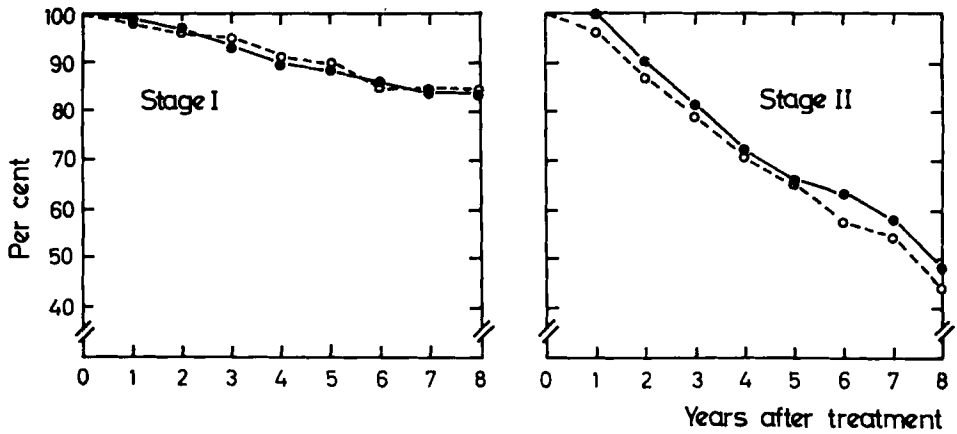

Fig. 1. Survival rates according to primary treatment. ○ Surgery and irradiation (n = 173 in stage I and 109 in stage II). ● Surgery alone (n = 172 in stage I and 92 in stage II).

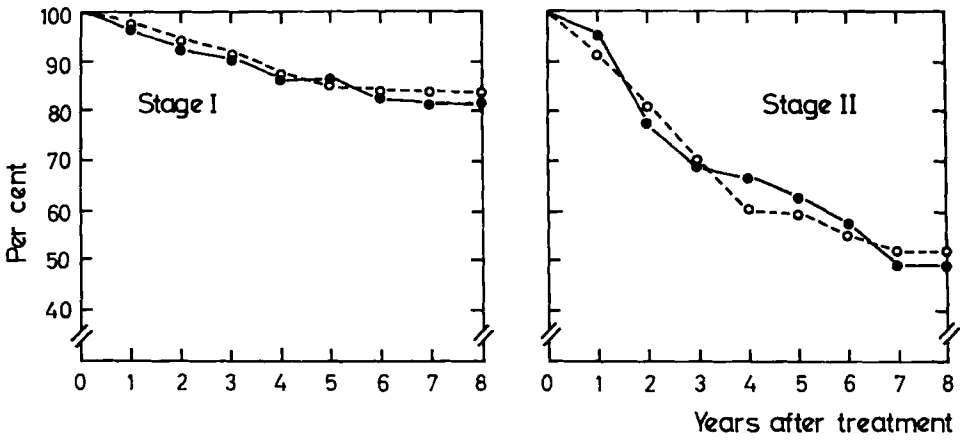

Fig. 2. Proportion of patients free from disease according to primary treatment. ○ Surgery and irradiation (n = 173 in stage I and 109 in stage II). ● Surgery alone (n = 172 in stage I and 92 in stage II).

among patients stage II in the control group, no distant metastases were observed within the first year after the primary treatment.

Discussion

Postoperative irradiation may be administered by different methods with variation of treatment fields and dosage. This may explain possible differences in the results. Evidence to support the value of postoperative irradiation as an adjuvant to radical mastectomy with axillary lymph node dissection is tenuous and only based

Table 1

Frequency of local recurrences

	Irradiated	Controls
Stage I	6/173 (3.5 %)	7/172 (4.0 %)
Stage II	9/109 (8.2 %)	14/92 (15.2 %)
Total	15/282 (5.7 %)	21/264 (8.0 %)

Table 2

Frequency of homolateral axillary metastases

	Irradiated	Controls
Stage I	2/173 (1.2 %)	1/172 (0.6 %)
Stage II	2/109 (1.8 %)	5/92 (5.4 %)
Total	4/282 (1.4 %)	6/294 (2.3 %)

Table 3

Frequency of homolateral supraclavicular lymph node metastases

	Irradiated	Controls
Stage I	1/173 (0.6 %)	5/172 (2.9 %)
Stage II	3/109 (2.8 %)	13/92 (14.1 %) $p < 1$ %
Total	4/282 (1.4 %)	18/264 (6.8 %) $p < 1$ %

Table 4

Time from primary treatment to appearance of first distant metastasis

Treatment group	Months following the primary treatment			Total number of patients with distant metastasis
	−11	12–23	24–	
Stage I				
Irradiated	2	5	17	24
Controls	4	5	14	23
Stage II				
Irradiated	9	10	27	46
Controls		16	24	40

upon data obtained retrospectively (HARRINGTON 1952, LEWISON & SMITH 1963, WATSON 1967). The results of two randomized prospective clinical trials (EASSON 1968, FISCHER et coll. 1968) did not indicate benefit from postoperative irradiation in terms of survival. In the Manchester trial two different types of radiation therapy were applied with the object of comparing the effect of irradiation administered immediately after surgery with that administered only when recurrences appeared. No significant difference in survival between the groups was encountered. Immediate postoperative irradiation reduced the incidence of local recurrence, but at the time of death the percentage of patients with uncontrolled local recurrence was almost identical in the two groups. A possible increase in the incidence of liver metastases was observed in the irradiated patients. Since only one-third of the controls required treatment at a later time for local recurrence, two-thirds of these patients were spared unnecessary irradiation.

In the National Surgical Adjuvant Project Protocol (NSABP), a randomized clinical trial (FISCHER et coll) designed to evaluate the value of postoperative irradiation to parasternal, axillary and supraclavicular fields a minimum of 3 500 rad in no more than 3 weeks or 4 500 rad in no more than 5 weeks was required. About 75 per cent of the patients received supervoltage irradiation and the remainder were given orthovoltage irradiation. This therapy reduced the number of regional metastases, but was without influence on disease-free and crude survival. The data suggested, however, that distant metastases occurred earlier in the irradiated group than in the control group.

The present results have clearly demonstrated that it is essential when discussing the value of postoperative irradiation in carcinoma of the breast to differentiate between patients in stage I and stage II. No effect of postoperative radiation in stage I as regards crude survival, disease-free survival, local recurrence, axillary lymph node or distant metastases was demonstrated. Homolateral supraclavicular lymph node metastases were, in fact, more frequent in the control group (2.9 %) than in the irradiated group (0.6 %).

In stage II postoperative irradiation significantly reduced the incidence of homolateral supraclavicular lymph node metastases.

Moreover, the proportion of patients with homolateral axillary lymph node metastases was less in the irradiated group (1.8 %) than in the control group (5.4 %). Local recurrence also occurred less frequently in the irradiated group (8.2 %) than in the control group (15.2 %), but postoperative irradiation had no influence on the incidence of distant metastases or on survival.

The effect of postoperative irradiation on the immunologic defence of patients with malignancy is not fully understood. Local radiation therapy could impair the cell-mediated immune response in patients with carcinoma of the breast by destroying lymphocytes. STJERNSVÄRD et coll. (1972) have demonstrated that irradiation of parasternal and supraclavicular fields in patients with carcinoma of the breast not only resulted in general lymphopenia of longstanding duration, but also that this

lymphopenia mainly affects the thymus dependent (T-) lymphocytes. Previous results (EASSON, FISCHER et coll.) also suggest that postoperative irradiation may increase the risk of distant metastases. In the present material distant metastases occurred in 9 irradiated cases in stage II within the first year against none in the control group, which might suggest that postoperative irradiation enhances the risk of distant metastases. However, in the controls stage I during the same period distant metastases occurred in 4 patients, i.e. twice as frequently as in the irradiated group. This impairs the significance of the findings in the stage II patients. Taken together, the results in stage I and stage II concerning time of occurrence of distant metastases are confusing and difficult to explain. The results in stage II patients may support the hypothesis that postoperative irradiation may suppress the immunologic defence and thereby increase the risk of distant metastases.

In the present material orthovoltage irradiation material only has been used and the dose to the skin and regional nodes has been rather small. Even though postoperative irradiation with this technique decreased the incidence of local recurrence and regional metastasis, it had no influence on the proportion of disease-free patients nor on the survival rate. Only every fifth of the controls in stage I and every second in stage II needed radiation at a later date because of recurrent disease. By giving up routine postoperative radiation with the employed technique particularly in stage I and using it later if need arises many patients with mammary carcinoma could be spared unnecessary radiation. However, different results may possibly be obtainable by other treatment fields and by increasing the dose, which will be discussed in Part II.

Acknowledgements

The authors are indebted to dr.phil. Knut Magnus for statistical advice and to Ashton Miller, M.D., F.R.C.S. for reviewing the manuscript.

SUMMARY

The effect of routine postoperative irradiation in the treatment of carcinoma of the breast has been evaluated. Postoperative irradiation had no effect on the proportion of patients free of disease nor on the survival rate, but the incidence of local recurrence and homolateral supraclavicular lymph node metastasis was reduced. In stage II patients homolateral axillary lymph node metastases were also encountered less frequently in the irradiated group. Distant metastases occurred earlier in stage II patients with postoperative irradiation as compared with controls.

ZUSAMMENFASSUNG

Der Effekt der routinemässig vorgenommenen postoperativen Bestrahlung bei der Behandlung des Brustkarzinoms wurde festgestellt. Die postoperative Bestrahlung hatte keinen Effekt auf den Anteil der Patienten, die frei von der Erkrankung waren oder auf die

Überlebensrate, jedoch war das Vorkommen lokaler Recidive und homolateraler supraclavikulärer Lymphknoten-Metastasen geringer. Bei Grad II Patienten wurden homolaterale Lymphknoten-Metastasen der Axilla ebenfalls weniger häufig in der bestrahlten Gruppe angetroffen. Fernmetastasen traten bei Grad II Patienten mit postoperativer Bestrahlung im Vergleich zu den Kontrollen häufiger auf.

RÉSUMÉ

Les auteurs ont étudié l'effet d'une irradiation post-opératoire systématique dans le traitement du cancer de sein. L'irradiation post-opératoire n'a pas d'effet sur la proportion de malades guéries ni sur le taux de survie, mais elle réduit la fréquence des récidives locales et des métastases ganglionnaires lymphatiques susclaviculaires homolatérales. Chez les malades du stade II les métastases ganglionnaires lymphatiques axillaires homolatérales ont aussi été moins fréquentes dans le groupe de malades irradiées. Les métastases à distance se sont produites plus tôt chez les malades du stade II ayant reçu une irradiation post-opératoire que chez les témoins.

REFERENCES

EASSON E. C.: Postoperative radiotherapy in breast cancer. *In:* Prognostic factors in breast cancer, p. 118. Edited by A. P. Forrest and P. B. Kunkler, E. & A. Livingstone, Edinburgh 1968.

FISCHER B., SLACK N. H., CAVANAUGH P. J., GARDNER B. and RAVDIN R. G.: Postoperative radiotherapy in the treatment of breast cancer: results of the NSABP clinical trial. Ann. Surg. 168 (1968), 337.

GUTTMANN R. J.: Radiotherapy in locally advanced cancer of the breast. Adjunct to standard therapy. Cancer 20 (1967), 1046.

HAAGENSEN C. D.: The treatment and results in cancer of the breast at Presbyterian Hospital, New York. Amer. J. Roentgenol. 62 (1949), 328.

HALSTED W. S.: The results of operations for the cure of cancer of the breast performed at the Johns Hopkin's Hospital from June, 1889, to January, 1894. Johns Hopk. Hosp. Rep. 4 (1894–95), 297.

HARRINGTON S. W.: Results of surgical treatment of unilateral carcinoma of the breast in women. J. Amer. med. Ass. 148 (1952), 1007.

LEWISON E. F. and SMITH R. I.: Results of breast cancer treatment at Johns Hopkins Hospital 1946–1950. Surgery 53 (1963), 644.

MARSHALL S. F. and HARE H. F.: Carcinoma of the breast: Results of combined treatment with surgery and roentgen rays. Ann. Surg. 125 (1947), 688.

NISSEN-MEYER R.: Castration as part of the primary treatment for operable female breast cancer. Acta radiol. (1965) Suppl. No. 249.

STJERNSVÄRD J., JONDAL M., VANKY F., WIGZELL M. and SEALY R.: Lymphopenia and change in distribution of human B and T lymphocytes in peripheral blood induced by irradiation for mammary carcinoma. Lancet (1972), 1352.

WATSON T. A.: Carcinoma of the breast. Stage II—radiation range. Can survival be increased by postoperative irradiation following radical mastectomy? J. Amer. med. Ass. 200 (1967), 136.