Ovarian irradiation and prednisone therapy following surgery and radiotherapy for carcinoma of the breast

J. WILLIAM MEAKIN, MD; WILLIAM E.C. ALLT, MD; FRANCIS A. BEALE, MD; THOMAS C. BROWN, MD; RAYMOND S. BUSH, MD; ROY M. CLARK, MD; PETER J. FITZPATRICK, MD; NIGEL V. HAWKINS, MD; R. DEREK T. JENKIN, MD; JOHN F. PRINGLE, MD; JOAN G. REID, MA; WALTER D. RIDER, MD; JOHN L. HAYWARD, FRCS; RICHARD D. BULBROOK, PH D

Following mastectomy, patients with operable breast cancer underwent postoperative irradiation of the chest wall and regional lymph nodes. They were then assigned at random to receive no further therapy, ovarian irradiation (2000 rads in 5 days) or ovarian irradiation in the same dosage plus prednisone, 7.5 mg daily. A total of 705 patients received the randomly assigned treatment and were followed for up to 10 years. In premenopausal patients who received ovarian irradiation the recurrence of breast cancer was delayed and survival prolonged, but not significantly. In premenopausal women aged 45 years or more ovarian irradiation plus prednisone therapy significantly delayed the recurrence of breast cancer ($P = 0.02$) and prolonged survival ($P = 0.02$); the survival expectancy of these patients was similar to that of the general population of the same age from the third year after the cancer operation. No value was demonstrated for ovarian irradiation with or without prednisone therapy in postmenopausal patients.

Des patientes porteuses d'un cancer du sein opérable reçurent, à la suite d'une mastectomie, de la radiothérapie au niveau de la cage thoracique et des ganglions régionaux. Elles furent ensuite réparties au hazard: les unes ne reçurent aucun autre traitement, les autres reçurent une irradiation des ovaires (2000 rads en 5 jours) ou la même dose en plus de la prednisone à 7.5 mg par jour. Un total de 705 patientes reçurent un traitement assigné au hazard et furent suivies durant une période allant jusqu'à 10 ans. Chez les patientes préménopausées qui reçurent l'irradiation des ovaires, la récidive fut retardée et la survie prolongée, mais pas de façon significative. Chez les femmes préménopausées ayant 45 ans ou plus l'irradiation des ovaires avec de la prednisone a produit un délai significatif de récidive ($P = 0.02$) et une prolongation de la survie ($P = 0.02$); l'espérance de vie de ces patientes était semblable à celle de la population générale du même âge à partir de la troisième année après la mastectomie. Aucune valeur n'a été démontrée quant à l'irradiation des ovaires avec ou sans prednisone chez les patientes postménopausées.

From the Princess Margaret Hospital and the University of Toronto (all but J.L.H. and R.D.B.) and the Imperial Cancer Research Fund and Guy's Hospital, London, England (J.L.H. and R.D.B.)

Presented in part at the First International Conference on the Adjuvant Therapy of Cancer, Tucson, Arizona, Mar. 2-5, 1977, and published in part in "Adjuvant Therapy of Cancer", SALMON SS, JONES SE (eds), North-Holland, Amsterdam, 1977, pp 95-99

Reprint requests to: Dr. J. William Meakin, 500 Sherbourne St., Toronto, Ont. M4X 1K9

In 1889 Schinzinger[1] suggested that oophorectomy might be useful in the primary treatment of patients with breast cancer, and in 1896 Beatson[2] demonstrated that bilateral oophorectomy was of value in controlling advanced breast cancer. In 1922 DeCourmelles[3] reported the first instances of destruction of the ovaries by irradiation in patients with breast cancer. In ensuing years retrospective studies stimulated much controversy about the value of prophylactic ovarian ablation.[4]

Several prospective clinical trials have been carried out to test the value of prophylactic ovarian ablation as part of the primary treatment of breast cancer. In the Manchester trial[5] ovarian irradiation (450 rads in one fraction) in premenopausal patients with or without histologic evidence of metastatic disease in the axillary lymph nodes delayed the appearance of distant metastases ($P = 0.04$) but did not significantly increase the 10-year survival rate ($P = 0.07$). In the Oslo trial[6] ovarian irradiation (1000 rads in six daily fractions) in premenopausal patients with histologic evidence of metastatic disease in the axillary nodes and postmenopausal patients without such evidence delayed the recurrence of breast cancer and increased the 7-year survival rate, but the differences were small. The National Surgical Adjuvant Breast Project[7] produced data suggesting that oophorectomy did not significantly delay recurrence or prolong life; the patients, who were premenopausal and had or did not have histologic evidence of meta-

static disease in the axillary nodes, were followed up for 3 to 5 years.

Nissen-Meyer[8] reported that prophylactic corticosteroid therapy and ovarian ablation prolonged life in a group of breast cancer patients of all ages. He further reported that the excretion of estrone in the urine of postmenopausal patients was reduced by the corticosteroid therapy. These observations, together with the well known value of prednisone in the treatment of recurrent breast cancer, led to the test of prednisone therapy reported in this paper.

Because of the ambiguous results of these trials the following study was carried out to test the hypothesis that prophylactic ovarian irradiation, with or without prednisone, would not only delay the recurrence of breast cancer but also prolong the life of patients with operable carcinoma of the breast.

Methods

Patient selection and initial management

From 1965 to 1972, patients aged 35 to 70 years who were referred to the Princess Margaret Hospital, Toronto within 10 days to 3 months after an operation for carcinoma of the breast (clinical stage I, II or operable III, according to the tumour–nodes–metastases classification of the International Union against Cancer[9]) were considered for the trial.

Patients were excluded for the following reasons: poor general health; previous or concurrent neoplasm (other than treated squamous or basal cell carcinoma); previous oophorectomy; prior antineoplastic chemical or hormonal therapy; contraindication to prednisone therapy (peptic ulcer, diabetes mellitus, chronic infection, mental illness, etc.); lack of consent from the referring doctor, the patient or the spouse; probable lack of availability for follow-up; and pregnancy within 1 year of the operation.

Any operation that removed the known local disease was acceptable. The most common procedure was mastectomy plus axillary dissection. Pathologic specimens were reviewed by one of us (T.C.B.); the findings will be reported separately.

Following clinical assessment and exclusion of metastatic disease, urine was collected for 24 hours from all patients less than 60 years of age for steroid hormone analysis and correlation of the results with the response to treatment. These observations will also be reported separately.

All patients then received postoperative irradiation (with cobalt-60; distance from source to skin, 80 cm) to the chest wall and regional lymph nodes, including the ipsilateral internal mammary chain. All fields were treated on alternate days except the internal mammary area, which was treated daily. The total dose of radiation, 4000 rads, was delivered in 16 treatment sessions during a 3-week period.

Allocation to experimental groups

The patients were then assigned at random to one of three regimens: no further treatment; ovarian irradiation; or, for women aged 45 years or more, ovarian irradiation and prednisone therapy. Patients less than 45 years old were not given prednisone because of concern that it might induce glucocorticoid toxic effects. Patients were stratified by age (less than 45 or 45 or older) and menstrual status. Patients were considered premenopausal if their last menses had occurred within 6 months of the operation. Patients who had had a hysterectomy but not an oophorectomy were considered premenopausal up to the age of 50 years. Stratification by axillary node status was not done, but this factor was considered in the analyses.

Further treatment

Ovarian irradiation was carried out with a cobalt-60 unit. The distance from skin to source was 80 cm, and 15 × 10-cm opposing fields were centred 2 cm above the upper edge of the symphysis pubis and in the midline. For 5 days 400 rads was given daily to the midplane (coronal) of the pelvis.

Prednisone was given orally in a dose of 2.5 mg three times daily. If side effects developed the dose was reduced, and if they were severe the drug was discontinued. In patients without recurrence of breast cancer, clinicians had the option of discontinuing prednisone after 5 years.

We advised against the use of other hormones or drugs that could theoretically affect the growth of residual tumour.

No restriction was placed on management after recurrence of the disease.

Follow-up

Patients were evaluated every 3 months for the first 2 years, every 6 months for the next 3 years and then once a year. When recurrence or death was reported by the attending clinician the hospital chart and roentgenograms were reviewed by two of us (J.W.M. and J.L.H.) and standardized criteria for establishing the existence and date of recurrence or death were applied. Recurrence was considered to exist and was dated if there was histologic proof or progressive physical or roentgenographic evidence, but not if there were only symptoms or hematologic or biochemical data. Periods of freedom from recurrence and survival were determined from the date of the operation.

Statistical methods

The two-sided Wilcoxon test[10] was used to determine the significance of differences in periods of freedom from recurrence and survival. All the graphs were prepared with the use of an actuarial life-table method. The chi-square test with Yates's correction was used elsewhere, as indicated.

Results

Of the 779 patients allocated at random to further treatment 23 were found to be ineligible according to the protocol and their data were omitted from all analyses. An additional 51 patients who were eligible for further treatment did not receive the randomly assigned treatment; their data are discussed in the section on "protocol violations". The following data relate to the remaining 705 patients

who, as of May 1977, were eligible for further treatment and received it, even though it may have been incomplete.

Table I—Characteristics of premenopausal patients with breast cancer less than 45 years old

Variable	Treatment* NT	R
Total group (no.)	73	77
Ineligible for further treatment according to protocol (no.)	3	2
Eligible but did not receive the randomly assigned treatment (no.)	0	8
Total evaluable group (no.)	70	67
Mastectomy with axillary dissection (%)	93	90
Mastectomy without axillary dissection (%)	7	9
Partial mastectomy (%)	0	1
Clinical stage (%)		
I	34	42
II	30	24
III	20	33
Not known	16	1
Axillary lymph nodes known to be involved (%)		
Any number	83	91
One to three	53	58
Four or more	29	30
Median age (yr)	42	41

*After removal of known local disease and irradiation of the chest wall and regional lymph nodes, patients received, by random allocation, no further treatment (NT), ovarian irradiation (R) or ovarian irradiation and prednisone (R + P).

Premenopausal patients less than 45 years of age

The salient clinical features of this group of patients are presented in Table I. Axillary lymph nodes were known to be involved in 91% of the group treated with ovarian irradiation and in 83% of those receiving no further treatment. Otherwise the composition of the two groups was similar.

The recurrence-free and survival curves for this group of patients, presented in Figs. 1A and 1B respectively, show that while ovarian irradiation delayed the recurrence of disease and prolonged survival the differences between the two treatment groups were not significant (P = 0.13 and 0.19 respectively). Separate analysis of the data for patients with involved axillary lymph nodes revealed a similar delay in recurrence and improvement in survival (P = 0.12 and 0.17 respectively). This indicates that the lack of a demonstrably greater effect of ovarian irradiation on recurrence rate and survival cannot be attributed to the higher proportion of patients with involved axillary lymph nodes in the treatment group.

Premenopausal patients 45 years of age or more

The salient clinical features of this group of patients are presented in Table II. The three treatment groups were similar with respect to type of operation, clinical stage, axillary node involvement and age.

The recurrence-free and survival curves for this group of patients are shown in Figs. 2A and 2B respectively. The data in Fig. 2A indicate that while ovarian irradiation with or without prednisone therapy delayed recurrence, only ovarian irradiation with prednisone therapy did so to a significant degree (P = 0.18 and 0.02 respectively). Separate analysis of the data for patients with involved axillary lymph nodes revealed a similar delay in recurrence (P = 0.04). In Fig. 2B it can be seen that both ovarian irradiation alone and ovarian irradiation with prednisone therapy prolonged survival but only the latter did so to a significant degree (P = 0.44 and 0.02 respectively). Separate analysis of the data for patients with involved axillary lymph nodes revealed a similar prolongation of survival (P = 0.65 and 0.06 respectively).

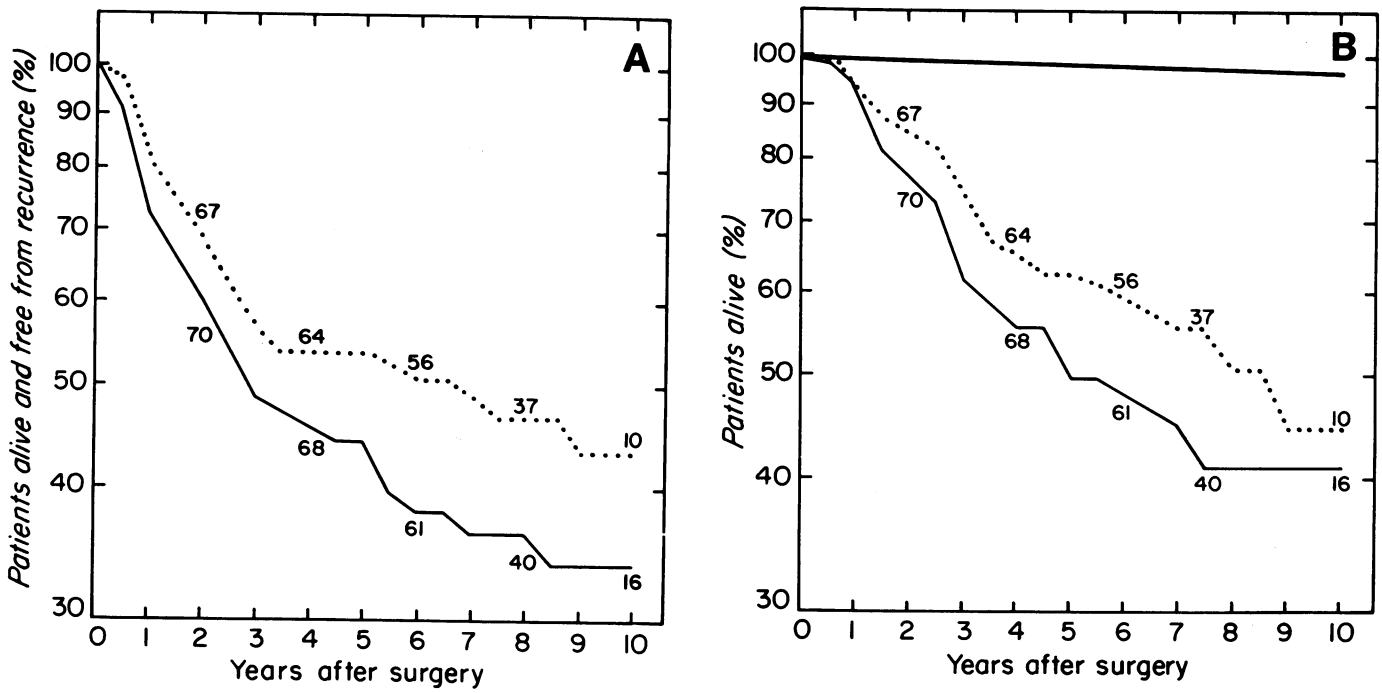

FIG. 1—Recurrence-free (A) and survival (B) curves for premenopausal patients with breast cancer less than 45 years old. After removal of known local disease and irradiation of chest wall and regional lymph nodes, patients received either no further treatment (NT; 70 patients; solid curve) or ovarian irradiation (R; 67 patients; dotted curve). Number of patients followed to specific times after operation are recorded. Curves not significantly different (P = 0.13 and 0.19 respectively). Natural survival for age range shown in heavy line at top of graph on right.

The slope of the survival curve with ovarian irradiation and prednisone therapy closely approximated the normal survival curve for this age group from about the third year after the operation. This indicates that a proportion of the patients treated in this manner have a normal survival expectancy.

All premenopausal patients

When the data on the recurrence-free period for the groups receiving no further treatment or ovarian irradiation were combined the difference between the resulting curves was found to be significant (P = 0.04), which indicated that ovarian irradiation alone had value in delaying recurrence. However, when the data on survival for the same two groups were combined the difference between the resulting curves was found not to be significant (P = 0.13), which indicated that ovarian irradiation did not prolong survival.

Postmenopausal patients

The salient clinical features of this group are presented in Table III. The three treatment groups were similar with respect to type of operation, clinical stage, axillary node involvement and age.

The recurrence-free and survival curves for this group of patients, shown in Figs. 3A and 3B respectively, indicate that ovarian irradiation with or without prednisone therapy did not significantly affect the recurrence-free interval or survival. Separate analysis of the data for patients with involved axillary lymph nodes produced similar results, as did separate analysis of the data for patients less than or more than 5 years from the menopause.

Survival of groups receiving no further treatment

The differences in the survival curves for these groups can probably be accounted for by differences in the status of the axillary lymph nodes. When this is considered the data approximate to those expected from the findings of Fisher and colleagues.[11]

Protocol violations

Data for patients who were eligible for further treatment but did not receive the randomly assigned treatment were subsequently included in

Table II—Characteristics of premenopausal patients with breast cancer aged 45 years or more

Variable	Treatment		
	NT	R	R + P
Total group (no.)	66	78	80
Ineligible for further treatment according to protocol (no.)	0	3	2
Eligible but did not receive the randomly assigned treatment (no.)	2	4	5
Total evaluable group (no.)	64	71	73
Mastectomy with axillary dissection (%)	95	90	95
Mastectomy without axillary dissection (%)	5	10	5
Partial mastectomy (%)	0	0	0
Clinical stage (%)			
I	47	49	52
II	19	21	18
III	26	26	26
Not known	8	4	4
Axillary lymph nodes known to be positive (%)			
Any number	69	66	71
One to three	41	44	40
Four or more	25	21	26
Median age (yr)	48	48	47

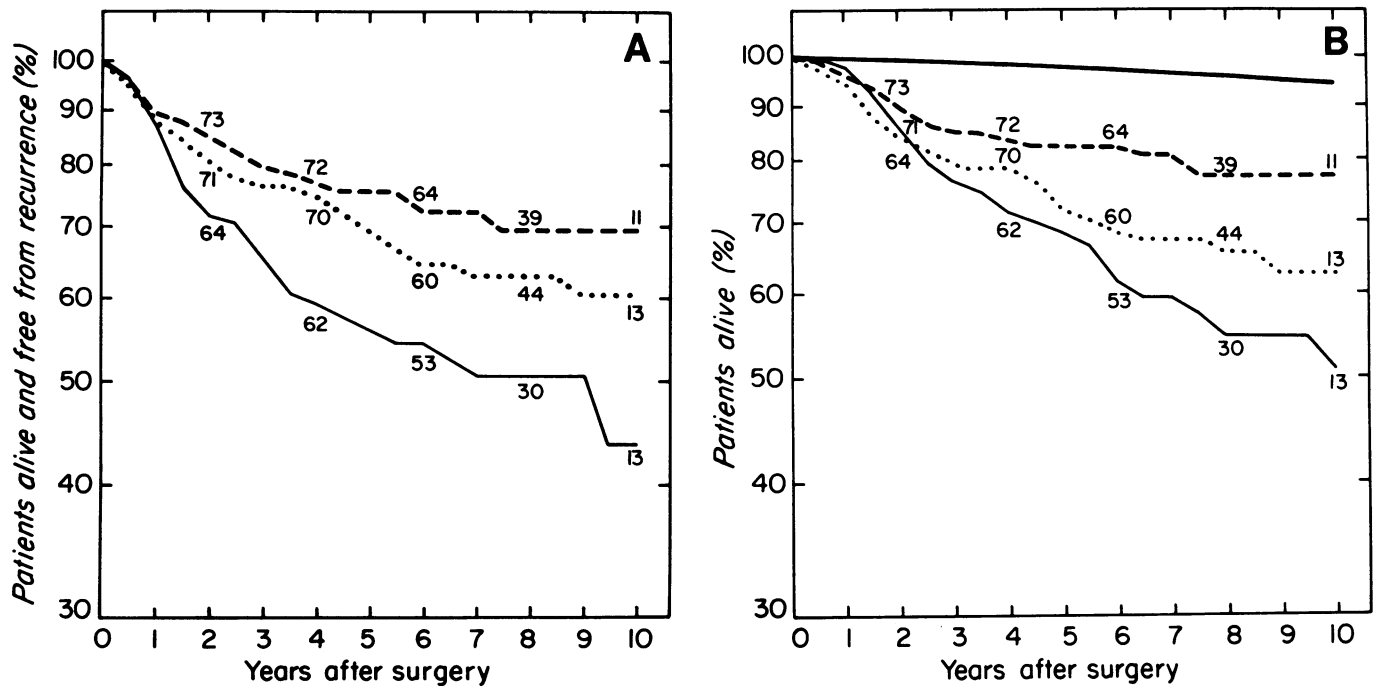

FIG. 2—Recurrence-free (A) and survival (B) curves for premenopausal patients with breast cancer aged 45 years or more. Number of patients in treatment groups: NT, 64; R, 71; ovarian irradiation and prednisone therapy (R + P), 73 (dashed curve). Curves not significantly different (A: NT v. R, P = 0.18; NT v. R + P, P = 0.02; R v. R + P, P = 0.31. B: NT v. R, P = 0.44; NT v. R + P, P = 0.02; R v. R + P, P = 0.11).

analyses. This did not affect the conclusions reached for the premenopausal patients less than 45 years of age or for the postmenopausal patients, but did affect the conclusions reached for the premenopausal patients aged 45 years or more, reducing the significance of the differences between no further treatment and ovarian irradiation with prednisone therapy to P = 0.07 from P = 0.02. The curves with no further treatment did not change appreciably, but those with ovarian irradiation and prednisone therapy were lowered.

Two patients assigned to no further treatment underwent ovarian ablation, and five patients assigned to ovarian irradiation and prednisone therapy either received only one of these treatments or received neither. The reasons for the protocol violations included a change in the wish of the patient or the referring doctor after treatment was randomly assigned and oversight by the clinical investigator. There was no evidence that the protocol violations were the result of investigator bias; therefore the observations regarding the value of ovarian irradiation and prednisone therapy remain valid.

Survival after recurrence

Some studies have indicated that prophylactic or adjuvant hormonal therapy may delay recurrence but lead to reduced survival after recurrence, so that overall survival is not changed.[4] We have demonstrated that this is not necessarily so, as a comparison of the curves for no treatment and ovarian irradiation with prednisone therapy (Fig. 2B) shows. Table IV emphasizes this point with estimated median survival times derived from actuarial graphs for survival from the time of first recurrence. The differences in survival were not significant except for that between the postmenopausal patients receiving no treatment and those receiving ovarian irradiation and prednisone therapy (P = 0.01). The reason for this difference is not clear at present.

Ovarian irradiation: dosage variation and toxicity

Of the 435 evaluable patients assigned to ovarian irradiation 15 received less than or more than the in-

Table III—Characteristics of postmenopausal patients with breast cancer

Variable	Treatment		
	NT	R	R + P
Total group (no.)	138	128	130
Ineligible for further treatment according to protocol (no.)	2	7	2
Eligible but did not receive the randomly assigned treatment (no.)	0	9	16
Total evaluable group (no.)	136	112	112
Mastectomy with axillary dissection (%)	82	84	88
Mastectomy without axillary dissection (%)	18	15	11
Partial mastectomy (%)	0	1	1
Clinical stage (%)			
I	46	54	42
II	17	20	17
III	32	22	34
Not known	5	4	7
Axillary lymph nodes known to be positive (%)			
Any number	60	70	63
One to three	40	44	34
Four or more	17	23	29
Median age (yr)	57	57	58

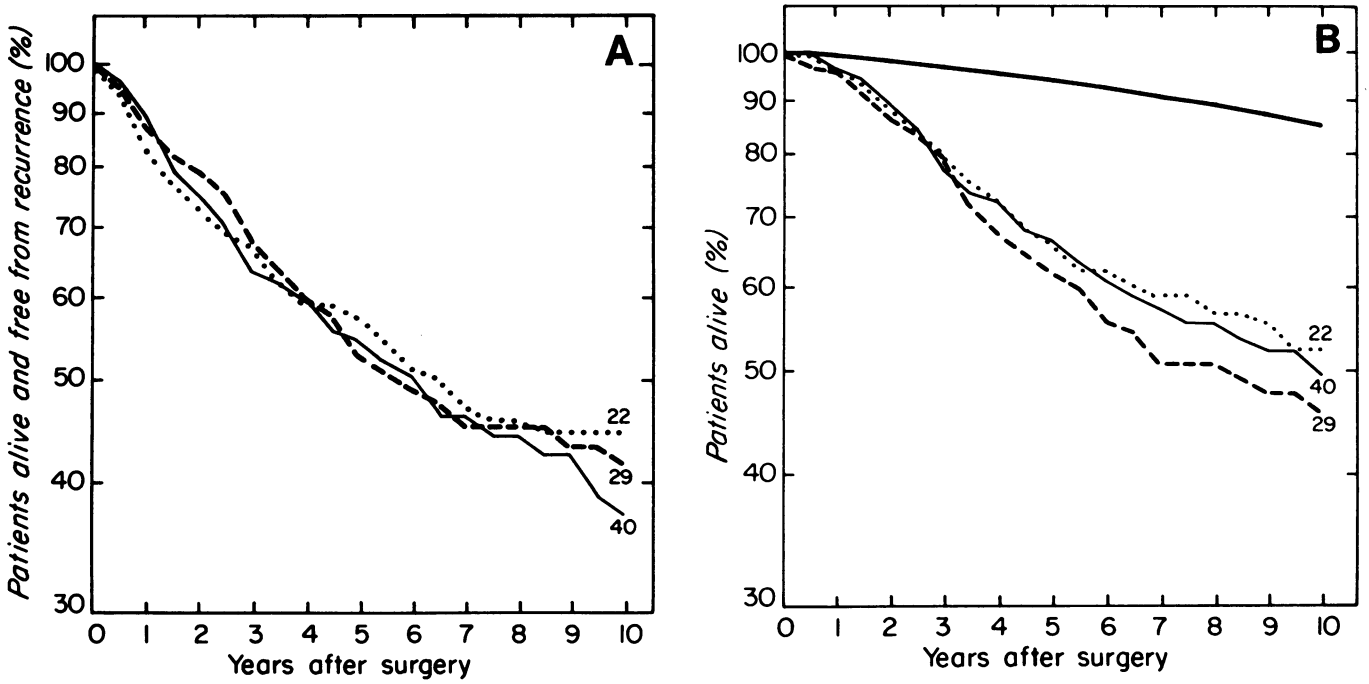

FIG. 3—Recurrence-free (A) and survival (B) curves for postmenopausal patients with breast cancer. Number of patients in treatment groups: NT, 136; R, 112; R + P, 112. Curves not significantly different.

Table IV—Estimated median survival after first recurrence of breast cancer

Experimental group	Survival (mo)
Premenopausal	
< 45 years old	
NT	10
R	12
≥ 45 years old	
NT	14
R	9
R + P	11
Postmenopausal	
NT	23*
R	18
R + P	11*

*P = 0.01 for significance of difference between actuarial curves from which median survival was estimated.

tended 2000 rads in 5 days: 2 received less than 1000 rads; 5, 1500 rads; 3, 1600 rads; 4, 1800 rads; and 1, 2400 rads. These variations were distributed in such a way that no effect on recurrence or survival in the entire group was likely.

Toxic effects were absent in 277 of the 435 patients receiving ovarian irradiation. Of the remainder 87 complained of flushing, 46 of transient diarrhea, 25 of transient vague abdominal discomfort, 15 of urinary frequency and 3 of rectal bleeding (1 had objective evidence of proctitis). Carcinoma of the ovary developed in one patient.

Return of menses after ovarian irradiation

Menses recurred following ovarian irradiation in 7% (5 of 67; median age 39 years) of the patients less than 45 years of age and in 1% (2 of 144; ages 45 and 48 years) of those over this age. All patients with return of menses had received the full 2000 rads to the ovaries in 5 days. Among the 144 aged 45 or older 73, including 1 of the 2 whose menses returned, received prednisone.

Prednisone: dosage variation and toxicity

Of the 73 premenopausal patients aged 45 years or more who were assigned to receive ovarian irradiation and prednisone 19 (26%) continued to receive prednisone without recurrence of breast cancer and 17 (23%) continued to receive prednisone until recurrence or death occurred. In the remaining 37 (51%) prednisone was discontinued prior to recurrence after a median duration of therapy of approximately 4 years. In the last group recurrence occurred in four patients; prednisone had been discontinued after 6 to 11 months of therapy in two patients, after 36 to 47 months in one patient; and after 48 to 59 months in one patient, and all of the recurrences occurred 2 or more years after prednisone therapy was stopped.

Of the 112 postmenopausal patients who were assigned to receive ovarian irradiation and prednisone 20 (18%) continued to receive prednisone without recurrence of breast cancer and 41 (37%) continued to receive prednisone until recurrence or death occurred. In the remaining 51 (46%) prednisone was discontinued prior to recurrence after a median duration of therapy of approximately 2 years. In the last group recurrence occurred in 17 patients; prednisone had been discontinued within 2 years in 12, and recurrence occurred within 2 years of the end of prednisone therapy in 9 patients.

Toxic effects were absent in 117 of 185 patients receiving prednisone. Of the remainder 23 complained of dyspepsia (1 had a peptic ulcer and 1 black stools), 21 noted facial fullness, 9 were thought to have some skeletal demineralization, 7 gained weight, 6 had "fluid retention" (lymphedema of the arm, ankle swelling or generalized fullness of tissues), 5 noted ease of bruising, 2 had elevated blood pressure, 2 had anxiety and depression and 1 was permanently dependent on prednisone. In general the attending staff felt that the degree of toxicity of prednisone was acceptable, though in some patients the toxic effects led to discontinuance of the drug.

Lymphocyte counts

Some authors have claimed that the absolute lymphocyte count in the peripheral blood predicts survival in patients with breast cancer. For most (712) of the patients in this study leukocyte and differential counts were done at the time of referral after the operation, before routine irradiation or ovarian irradiation with or without prednisone therapy. No correlation could be demonstrated between the lymphocyte count and the interval before recurrence.

Pattern of recurrence

The pattern of recurrence of both local (within and without the irradiated area) and distant disease is being analysed and the results will be published separately.

Discussion

The data from this study are in agreement with those from the Manchester[5] and Oslo[6] trials in demonstrating some delay in recurrence of breast cancer but no significant prolongation of survival with adjuvant ovarian irradiation.

The lack of agreement with the results of the National Surgical Adjuvant Breast Project,[7] in which a trial of prophylactic oophorectomy was conducted, is possibly due to chance or the fact that irradiation of the ovaries may result in a different physiologic state from that after surgical oophorectomy. Further follow-up data from the project may demonstrate some value for surgical oophorectomy, for in our study the effect of ovarian ablation did not become evident until after 3 to 5 years of follow-up.

However, our data indicate that small doses of prednisone in addition to ovarian irradiation produced a significant delay in recurrence and prolongation of survival in premenopausal patients aged 45 years or more. Furthermore, the survival of this group was approaching the normal survival from about the third year after the operation, though this may have been due in part to the exclusion from the trial of patients with unfavourable diseases (e.g., diabetes mellitus). However, in contrast was the steady rate of death in the group that received no further treatment; these patients would not be expected to achieve normal survival until 20 years after the operation, according to the data of Brinkley and Haybittle.[12]

Whether the prednisone produced its effect by suppressing the adrenal

secretion of estrogen or by some other mechanism is not known. Other possible mechanisms include a reduction in prolactin secretion (perhaps mediated by reduced estrogen production), immunologic factors and direct antitumour effects. Again we emphasize that the benefit of ovarian irradiation with prednisone therapy did not become definite until after 3 to 5 years of follow-up. It is not evident from this trial how long prednisone therapy should be continued; a longer period of therapy might have resulted in an even greater effect. While the value of prednisone therapy in addition to ovarian irradiation was not tested in patients less than 45 years of age, it is not unreasonable to expect that a similar effect would have been achieved in this group.

One important feature of the data from this study is that the combination of ovarian irradiation and prednisone therapy was effective in patients with involved axillary lymph nodes. The early data for adjuvant therapy with melphalan[13] and with a combination of cyclophosphamide, methotrexate and 5-fluorouracil[14] suggest degrees of benefit comparable to those observed in this study. Indeed, it may be that adjuvant cytotoxic chemotherapy produces some or all of its benefit through a hormonal mechanism such as ovarian suppression, particularly since the principal value of these regimens is observed only in premenopausal patients. Thus, it seems rational in future studies to examine the role of adjuvant hormonal therapy as a complement or an alternative to adjuvant cytotoxic chemotherapy.

We are indebted to the many surgeons who agreed to the entry of their patients into this study, to Drs. A.J. Phillips, A.H. Sellers and G. DeBoer for their biostatistical help, to Drs. A. Alaton and the late Dr. E. Kruyff for their assistance in the initial clinical assessment of the patients, and to the clinical trial secretaries, who helped monitor the study.

This study was supported by the Ontario Cancer Treatment and Research Foundation and the Imperial Cancer Research Fund.

References

1. Schinzinger A: Über Carcinoma mammae. *Verh Dtsch Ges Chir* 18: 28, 1889
2. Beatson GT: On the treatment of inoperable cases of carcinoma of the mammary: suggestions for a new method of treatment, with illustrative cases. *Lancet* 2: 104, 1896
3. DeCourmelles FV: La radiothérapie indirecte, ou dirigée par les corrélations organiques. *Arch Elect Med* 32: 264, 1922
4. Hayward JL: Hormones and breast cancer, in *Recent Results in Cancer Research,* vol 24, Springer-Verlag, Berlin, 1970, p 15
5. Cole MP: Suppression of ovarian function in primary breast cancer, in *Prognostic Factors in Breast Cancer,* Forrest APM, Kunkler PB (eds), Livingstone, Edinburgh, 1968, p 146
6. Nissen-Meyer R: Suppression of ovarian function in primary breast cancer. Ibid, p 139
7. Ravdin RG, Lewison EF, Slack NH, et al: Results of a clinical trial concerning the worth of prophylactic oophorectomy for breast cancer. *Surg Gynecol Obstet* 131: 1055, 1970
8. Nissen-Meyer R: Prophylactic endocrine treatment of carcinoma of the breast. *Clin Radiol* 15: 152, 1964
9. International Union Against Cancer: *TNM Classification of Malignant Tumours,* Geneva, 1968
10. Gehan EA: A generalized Wilcoxon test for comparing arbitrarily singly-sensored samples. *Biometrika* 52: 203, 1965
11. Fisher B, Slack N, Katrych D, et al: Ten year follow-up results of patients with carcinoma of the breast in a co-operative clinical trial evaluating surgical adjuvant chemotherapy. *Surg Gynecol Obstet* 140: 528, 1975
12. Brinkley D, Haybittle JL: The curability of breast cancer. *Lancet* 2: 95, 1975
13. Fisher B, Redmond C, et al: Studies of the National Surgical Adjuvant Breast Project (NSABP), in *Adjuvant Therapy of Cancer,* Salmon SS, Jones SE (eds), North-Holland, Amsterdam, 1977, p 67
14. Bonadonna G, Rossi A, Valagussa A, et al: Adjuvant chemotherapy with CMF in breast cancer with positive axillary nodes. Ibid, p 83

BOOKS

This list is an acknowledgement of books received. It does not preclude review at a later date.

CLINICAL LABORATORY STATISTICS. 2nd ed. Roy N. Barnett. 237 pp. Illust. Little, Brown and Company (Inc.), Boston, 1979. $17.50. ISBN 0-316-08196-5

CLINICAL THERAPEUTICS. Edited by David T. Lowenthal and David A. Major. 424 pp. Illust. Grune & Stratton, Inc., New York; Longman Canada Limited, Don Mills, Ont., 1978. $48.15. ISBN 0-8089-1080-9

continued on page 1238