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Locally Advanced Breast Cancer: The Contribution of Cytotoxic and Endocrine Treatment to Radiotherapy

An EORTC Breast Cancer Co-operative Group Trial (10792)*

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Abstract—*Patients with locally advanced carcinoma of the breast were randomized to receive either radiotherapy alone, radiotherapy + endocrine therapy, radiotherapy + chemotherapy or radiotherapy + endocrine therapy + chemotherapy. In 363 evaluable patients, time to first progression was delayed significantly by both endocrine treatment and chemotherapy, the greatest effect being achieved by the combination of endocrine treatment and chemotherapy. This effect was almost entirely due to a major effect of systemic treatment on time to loco-regional progression, for which the result is highly significant, rather than time to distant metastasis in which only a non-significant trend was observed. For survival, a trend was seen in favour of the combination of hormone treatment and chemotherapy, but this effect did not achieve statistical significance. This trial suggests that current endocrine and cytotoxic treatments are only of marginal value in improving the prognosis in locally advanced breast cancer.*

INTRODUCTION

PRIMARY locally advanced breast cancer is characterized by the presence of one or more of the following features: infiltration of overlying skin, satellite skin nodules, extensive peau d'orange, attachment to deep structures, tethering or fixation of axillary nodes, involvement of supraclavicular nodes. This stage of the disease accounts for 10–20% of patients presenting with breast cancer in Western Europe and North America, but for the majority in developing countries. It corresponds approximately to stage III on the TNM classification [1] in which is included T3,4,N(any), M0 or T(any),N2,3,M0 tumours. This does, however, contain some operable tumours (T3a,N0,1,M0) which are included in this category only because of the large size of the primary tumour. The other categories in stage III, namely T3b,4,N0,1,M0 or T0–4,N2,3,M0 are usually considered inoperable and treated by radiotherapy. Operable stage III tumours have a significantly better prognosis than inoperable disease [2]. Nevertheless, in cancers which are technically operable, involvement of the highest axillary lymph node (apex node) is associated with a particularly poor prognosis after mastectomy [3]. Hence, apex node biopsy has been recommended as part of the staging procedures for breast cancer and, when positive, radiotherapy rather than surgery has been adopted as the preferred treatment in some centres.

Several analyses on prognostic factors in locally advanced inoperable disease have been done [4–6]. Favourable factors include a long duration of symptoms (>6 months) before presentation, deep fixation of the primary tumour, a good response to primary radiotherapy and the rendering of initially inoperable disease suitable for mastectomy. Unfavourable factors are the early postmenopausal years (1–5 years since last menstrual period), a short duration of symptoms before presentation (<6 months), diffuse primary tumours and inflammatory carcinoma. In inoperable locally advanced disease, the size of the primary tumour and the presence or absence of skin involvement are probably neutral factors. It is possible to use these covariates in a multivariate

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analysis which shows that, by weighting the variables appropriately, groups of patients with significantly differing prognoses can be identified within the general grouping of locally advanced disease [5]. This emphasizes the importance of considering these variables in analysis of clinical trials.

Although the disease is localized at presentation, there is a high incidence of subsequent distant metastases in patients with stage III tumours and in one series this was almost 70% [5]. This accounts for the poor prognosis of patients treated by radiotherapy alone. In a literature survey of 1800 patients, the 5-year survival was only 21.5% [7]. This led to the study of cytotoxic chemotherapy combined with radiotherapy for the primary treatment of these patients. Two studies showed that locally advanced breast tumours are chemosensitive with a response frequency of about 70% and historical comparisons suggested that survival could be improved by this approach [8, 9], but a controlled clinical trial did not support these tentative conclusions [10].

The object of this study has been to test in a prospective randomized controlled clinical trial the contribution of cytotoxic chemotherapy and endocrine therapy to radiotherapy in the primary treatment of locally advanced breast cancer. Most patients had one or more of the features of locally advanced inoperable disease, but some were included on the basis of a positive apex node biopsy alone. The trial used a 2 × 2 factorial design (Fig. 1) in which radiotherapy is the initial treatment for all patients and common to all arms of the trial. Radiotherapy alone is the control against which the combined treatments, radiotherapy + endocrine and/or chemotherapy, are compared.

RADIOTHERAPY	RADIOTHERAPY + CHEMOTHERAPY
RADIOTHERAPY + ENDOCRINE THERAPY	RADIOTHERAPY + CHEMOTHERAPY + ENDOCRINE THERAPY

Fig. 1. Design of the 2 × 2 trial to assess contribution of cytotoxic chemotherapy, endocrine therapy, and combined cytotoxic and endocrine therapy to radiotherapy in the primary treatment of locally advanced breast cancer.

PATIENTS AND METHODS

Eligible patients were <70 years of age and had histologically confirmed breast cancer characterized by one or more of the following features: oedema of more than 1/3 of the skin over the breast; satellite tumour nodules in the skin of the affected breast; diffuse primary carcinoma; fixation of the tumour to underlying chest wall (pectoral fixation alone did not constitute evidence of locally advanced disease); skin infiltration greater than the diameter of the tumour; skin ulceration (except that associated with Paget's disease of the nipple); oedema of the ipsilateral arm; attachment of axillary lymph nodes to skin or chest wall; involvement of supraclavicular, infraclavicuar or internal mammary lymph nodes, which must have been confirmed histologically if they were in isolation. Patients with histologically proven apex node involvement from centres where routine biopsies were done were eligible in the absence of any other features of locally advanced disease.

Patients were excluded if there was evidence of distant tumour spread. In the case of a positive bone scan this did not lead to exclusion unless suspicious lesions were confirmed radiologically. Patients had had no previous operative, systemic or radiation treatment for breast cancer, other than biopsy for confirmation of the diagnosis. Patients who were pregnant or had had previous or concomitant malignant disease were excluded, except for previously adequately treated squamous cell or basal cell carcinoma of the skin or *in situ* carcinoma of the cervix uteri. Patients currently receiving systemic corticosteroid therapy or who had done so in the previous year were not eligible.

Patients had a full history taken with particular attention to menstrual status and the duration of symptoms. A full physical examination was undertaken with particular attention to the size of the primary tumour or its diffuseness, skin involvement, deep attachment and the characteristics of regional lymph node involvement. Bilateral mammography was performed and biopsy for histological confirmation and, in a proportion of patients, steroid receptor analysis was taken. All palpable lesions were measured in two perpendicular axes and photographs of visible lesions taken. A chest radiograph and either a radiological skeletal survey or an isotopic bone scan were performed. In the case of the latter, radiographs were taken of areas of increased radio-nuclide accumulation. Patients had a baseline full blood count and a biochemical screen to include creatinine, urea, bilirubin, transaminases, calcium and alkaline phosphatase. An isotopic liver scan or ultrasound scan of the liver was performed if liver biochemistry was abnormal.

Patients were randomly allocated to one of four treatment groups: (1) radiotherapy alone, (2) radio-

therapy + endocrine therapy, (3) radiotherapy + chemotherapy, (4) radiotherapy + endocrine therapy + chemotherapy (Fig. 1). Randomization was done before radiotherapy was started. Radiotherapy was standard for all four treatment groups, as was the endocrine treatment and chemotherapy in those groups to which it applied.

Before randomization, patients were stratified according to menstrual status. Premenopausal patients were defined as those whose last menstrual period occurred within the previous 6 months. Postmenopausal patients were those whose last menstrual period was 6 months or more ago. In patients who had had previous gynaecological surgery, those with both ovaries removed were considered postmenopausal. Patients <45 years of age who had had a previous hysterectomy with one or both ovaries retained were considered premenopausal, while those aged 55 years or more who had a previous hysterectomy were considered postmenopausal irrespective of whether or not ovaries were removed. Patients between 45 years and 55 years of age who had had a hysterectomy with one or both ovaries retained were excluded from the trial.

Radiotherapy was started within 2 weeks of the completion of baseline investigations. It was given by megavoltage to the whole breast, chest wall and the axillary, supraclavicular, infraclavicular and ipsilateral internal mammary nodes. The breast and chest wall were treated by planned glancing fields to a prescribed dose of 46 Gy in 23 fractions, the maximum dose not exceeding this by more than 10%. The axillary (central dose) and supraclavicular (peak dose) regions were treated in continuity by semi-opposed fields which were adjacent to and matched the edges of the breast and chest wall fields; the prescribed dose was 46 Gy in 23 fractions. Treatment continued with boosts of 14 Gy in 7 fractions to sites of initially palpable disease. Bolus was not used.

Within 2 weeks of the completion of radiotherapy, patients were reassessed clinically pending further treatment according to randomization. Those allocated to receive endocrine treatment and/or chemotherapy started systemic treatment within 4 weeks of the completion of radiotherapy.

For patients randomized to receive endocrine therapy this depended upon menstrual status. Premenopausal patients received ovarian irradiation (15 Gy) central dose, in 5 consecutive days by opposed fields + prednisolone 2.5 mg tds for 5 years, starting on the first day of ovarian irradiation. Postmenopausal patients were prescribed tamoxifen 10 mg bd for 5 years. When steroid receptor status was known, this was not considered for the selection of treatment in this trial and patients received the treatment to which they were randomized irrespective of steroid receptor status.

Patients randomized to receive chemotherapy were given 12 cycles of a combination of cyclophosphamide, methotrexate and 5-fluorouracil (CMF) as follows: cyclophosphamide 100 mg/m^2 (maximum 150 mg) orally on days 1–14, methotrexate 30 mg/m^2 (maximum 50 mg) i.v. (20 mg/m^2 for patients aged 60 years of age or more; maximum 40 mg) on days 1 and 8 and 5-fluorouracil 600 mg/m^2 i.v. (400 mg/m^2 for patients 60 years of age or more) (maximum 1000 mg) on days 1 and 8. No cytotoxic drugs were given on days 15–28; treatment was resumed on day 29 for a total of 12 courses of cytotoxic treatment. Blood counts were repeated before each course of chemotherapy was due. Provided the total white blood cell count was $\geq 4 \times 10^9$/l and the platelet count $\geq 120 \times 10^9$/l, full doses of drugs were given. For a total white blood cell count between 2 and 3.9×10^9/l or a platelet count between 70 and 119×10^9/l the doses of cytotoxic drugs were reduced to 50%. For a total white blood cell count $\leq 1.9 \times 10^9$/l or platelet count $\leq 69 \times 10^9$/l, cytotoxic drugs were omitted until repeat counts permitted at least 50% doses to be given.

In patients randomized to receive both endocrine therapy and chemotherapy, these treatments were started concomitantly.

For the first year, clinical assessment was done every 4 weeks. Thereafter, assessment was at 3-monthly intervals. The chest radiograph and isotopic or radiographic bone survey were repeated at 6-monthly intervals. This follow-up programme was continued until progressive disease developed.

In the event of progressive disease, treatment was not specified in the trial protocol. However, it was suggested that patients treated by radiotherapy alone should receive endocrine treatment followed by chemotherapy on further progression. Patients treated by radiotherapy and endocrine therapy were recommended to have chemotherapy and patients treated by radiotherapy and chemotherapy should have received endocrine therapy. Local relapse could be treated by further radiotherapy or surgery as considered appropriate; mastectomy was never done at the time of initial treatment.

The trial was assessed by time to progressive disease (local and distant) and survival. Time to loco-regional progression was taken from the date of randomization to the date of first observation of ipsilateral progressive disease within the region defined by the upper border of the trapezius superiorly, the mid sternal line medially, the costal margin inferiorly and the posterior axillary line laterally. Time to distant progression was from the date of randomization to the date of first observation of progressive disease outside the region defined above. Survival was from the date of randomization to death. The records of patients in this trial were subjected to extramural review.

Time to progression and duration of survival curves were calculated using Kaplan–Meier product limit estimate and were compared using the log-rank test and, for ordered variables, the log-rank test for trend. Treatment comparisons were adjusted for other factors by means of retrospective stratification.

RESULTS

Four hundred and ten patients from eight centres were entered into the trial between December 1979 and November 1985 of whom 363 are evaluable. Forty-seven patients were not evaluable for the following reasons: 37 were ineligible (30 for incorrect disease stage, five had previous treatment not allowed by the protocol and two had associated chronic disease); five were not evaluable due to major protocol infringements; five were entered by three institutions that were excluded for quality control reasons.

In the evaluable patients, a few errors in treatment assignment were identified. Nevertheless, in the ensuing analyses, patients are considered only within the groups to which they were randomized.

The characteristics of the patients, primary tumours and regional lymph nodes are shown in Tables 1, 2 and 3 respectively; all features are evenly distributed between the four treatment groups.

Time to disease progression

Time to first progression, either loco-regional or distant, was delayed significantly by both endocrine treatment and chemotherapy with the greatest effect being achieved by the combination of endocrine treatment and chemotherapy (Fig. 2). This effect is due almost entirely to a major effect of systemic treatment on time to loco-regional progression for which the result is highly significant (Fig. 3) rather than time to distant metastases in which only a non-significant trend is observed (Fig. 4).

The independent effects of hormone treatment and chemotherapy on time to loco-regional progression are shown in Figs. 5 and 6 respectively. In 36 patients these recurrences occurred after the appearance of distant metastases. The local effects of systemic treatment were seen in both pre- and postmenopausal women, but were more pronounced in the latter (for endocrine treatment: premenopausal $P = 0.08$, postmenopausal $P = 0.0001$; for chemotherapy: premenopausal $P = 0.1$, postmenopausal $P = 0.004$). The effect of endocrine treatment on time to loco-regional progression was significant only in patients with oestrogen receptor positive tumours (Fig. 7), while the effect of chemotherapy was more marked in patients with oestrogen receptor negative tumours (Fig. 8).

Univariate analyses using the log-rank test showed the following factors adversely to predispose to locoregional recurrence: postmenopausal status ($P = 0.03$), presence of skin oedema ($P = 0.001$), diffuse carcinoma ($P = 0.02$), inflammatory disease ($P = 0.04$), axillary node involvement ($P = 0.02$), supraclavicular node involvement ($P = 0.05$), oestrogen receptor level <10 fmol/mg cytosol protein ($P = 0.04$). Age, the presence of skin nodules, skin infiltration or ulceration chest wall involvement, tumour size or oedema of the arm were neutral factors. A detailed report on prognostic factors including a multivariate analysis will appear elsewhere.

Table 1. Characteristics of patients

	Radiotherapy	Radiotherapy + endocrine therapy	Radiotherapy + chemotherapy	Radiotherapy + endocrine therapy + chemotherapy	Total
Number of patients	91	92	88	92	363
Age					
No. ≤40 years	7	9	8	8	32
41–49 years	19	22	18	20	79
50–55 years	17	16	20	17	70
56–65 years	41	35	31	30	137
66–69 years	6	8	8	15	37
70–80 years	1	2	3	2	8
Menstrual status					
Premenopausal	32	34	34	38	138
Postmenopausal	59	58	54	54	225

Table 2. Characteristics of primary tumour

	Radiotherapy	Radiotherapy + endocrine therapy	Radiotherapy + chemotherapy	Radiotherapy + endocrine therapy + chemotherapy	Total
Number of patients	91	92	88	92	363
T0	0	0	2	0	2
T1	3	2	5	5	15
T2	21	28	18	23	90
T3	35	22	24	23	104
T4	27	34	34	36	131
Percentage with diffuse carcinoma	26	24	15	23	22
Percentage with skin infiltration	51	47	48	53	50
Percentage with skin nodules	9	13	6	10	10
Percentage with skin ulceration	10	10	6	15	10
Percentage with skin oedema	44	48	40	43	44
Percentage inflammatory	15	14	13	12	13
Percentage with chest wall involvement	7	9	6	9	8
Oestrogen receptor content (fmol/mg cytosol protein)					
0–10	22	18	18	20	78
11–100	16	24	21	21	82
>100	10	11	8	13	42
Unknown	43	39	41	38	161

Table 3. Characteristics of regional lymph nodes

	Radiotherapy	Radiotherapy + endocrine therapy	Radiotherapy + chemotherapy	Radiotherapy + endocrine therapy + chemotherapy	Total
Number of patients	91	92	88	92	363
N0	14	10	20	18	62
N1A	8	3	6	2	19
N1B	27	29	20	27	103
N2	16	16	13	11	56
N3	24	31	27	32	114
Percentage with axillary node involvement	81	78	76	74	77
Percentage with axillary nodes attached	18	13	15	16	15
Percentage with arm oedema	6	7	2	2	4
Percentage with supra-clavicular involvement	13	14	12	17	14
Percentage with infra-clavicular involvement	1.5	0	5	0	1.4

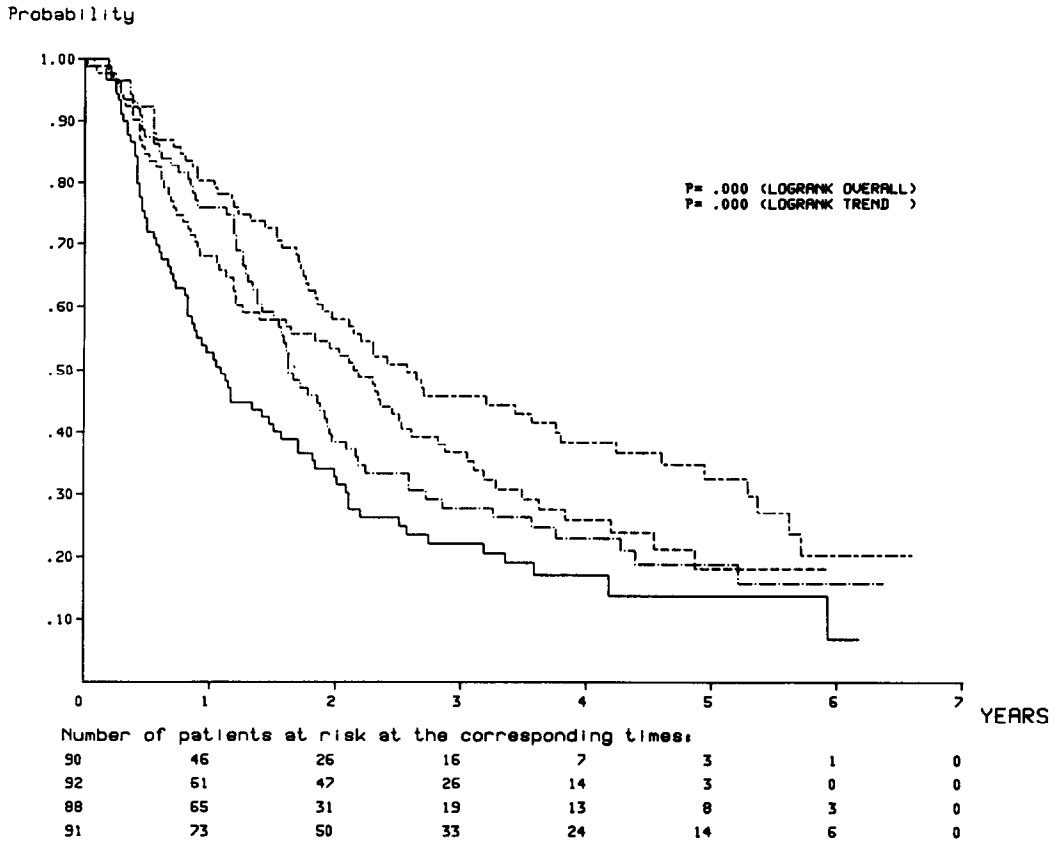


Fig. 2. Time to disease progression (—— radiotherapy alone; ----- radiotherapy + endocrine therapy; -·-·- radiotherapy + chemotherapy; —·— radiotherapy + endocrine therapy + chemotherapy).

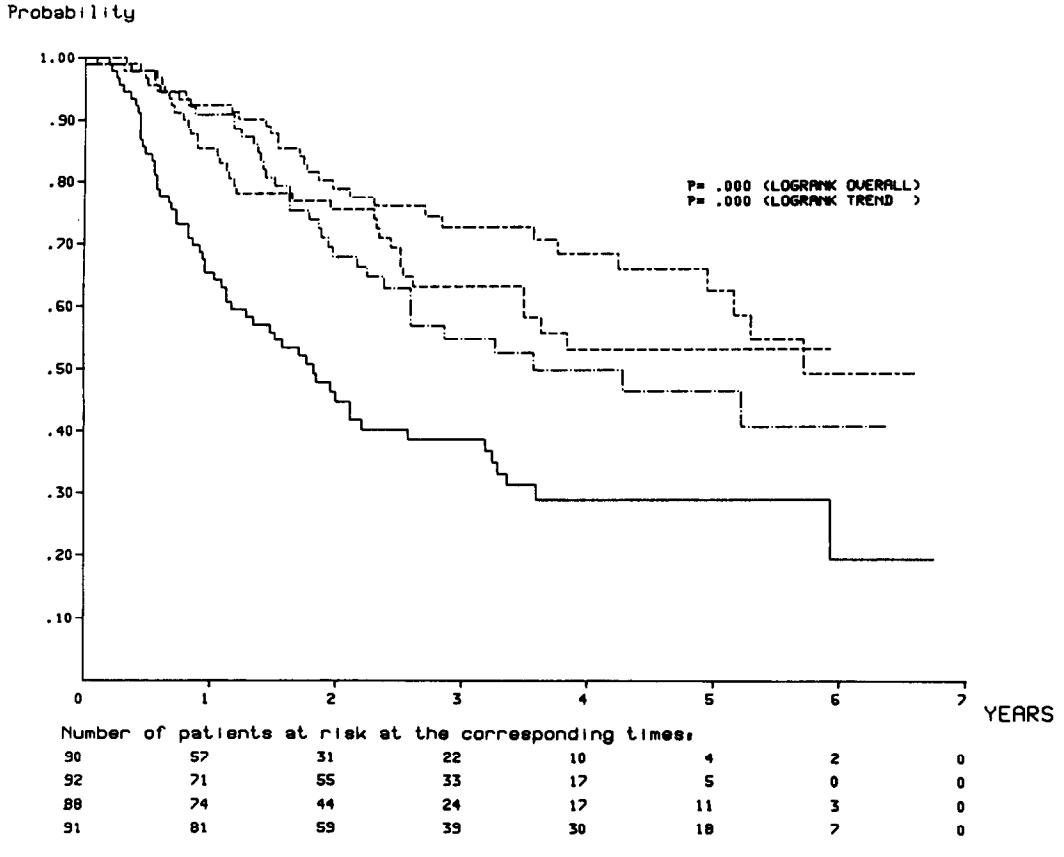


Fig. 3. Time to loco-regional progression (—— radiotherapy alone; ----- radiotherapy + endocrine therapy; -·-·- radiotherapy + chemotherapy; —·— radiotherapy + endocrine therapy + chemotherapy).

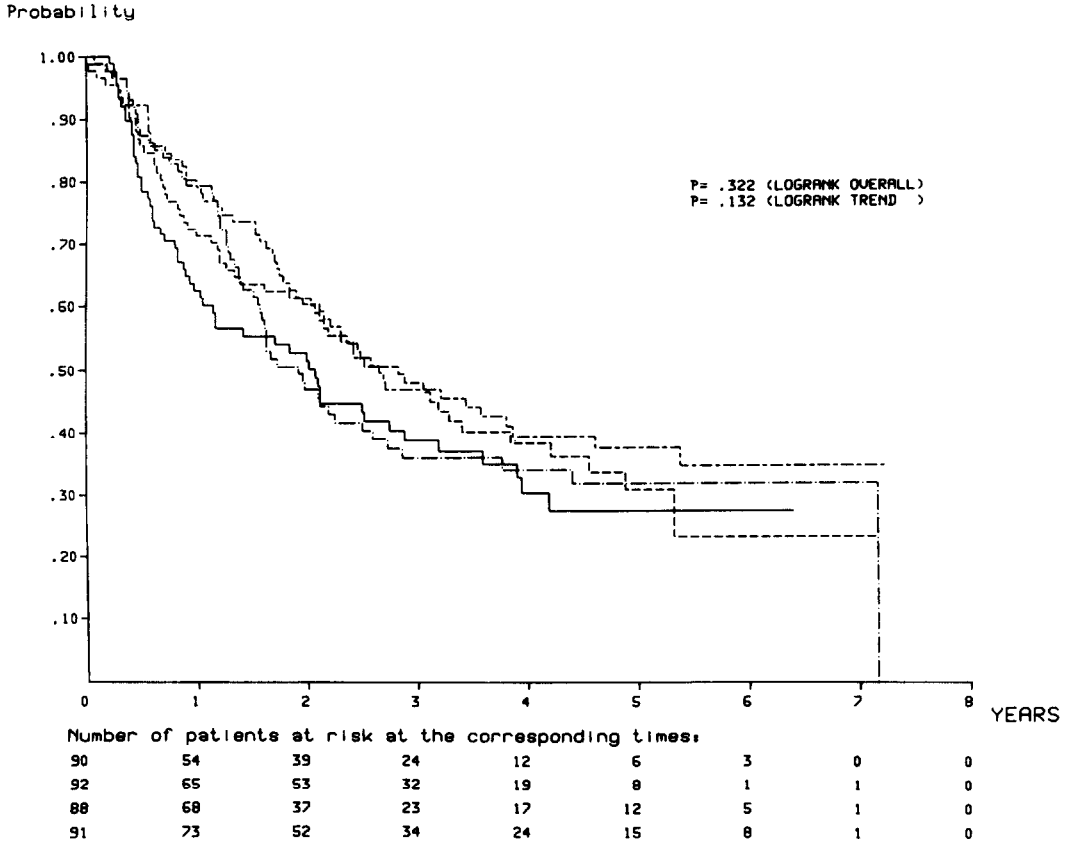


Fig. 4. Time to distant metastases (—— radiotherapy alone; ----- radiotherapy + endocrine therapy; –·–·– radiotherapy + chemotherapy; —·— radiotherapy + endocrine therapy + chemotherapy).

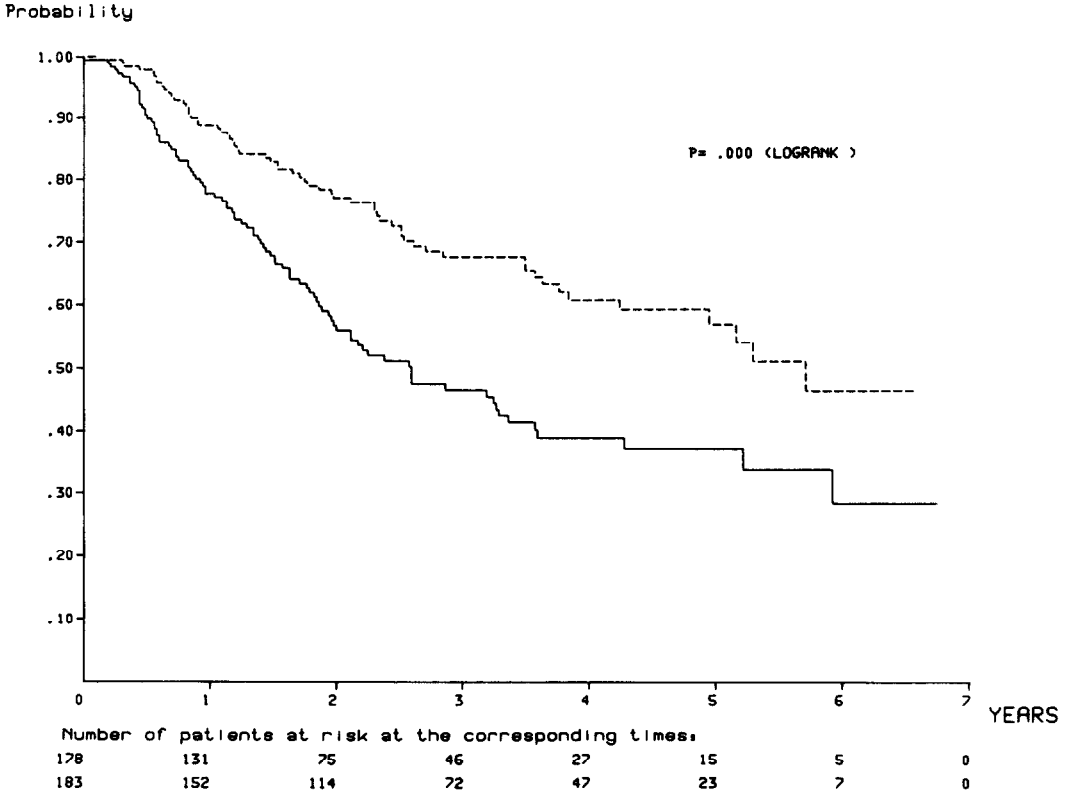


Fig. 5. Effect of endocrine therapy on time to loco-regional progression (—— no endocrine therapy; ----- with endocrine therapy).

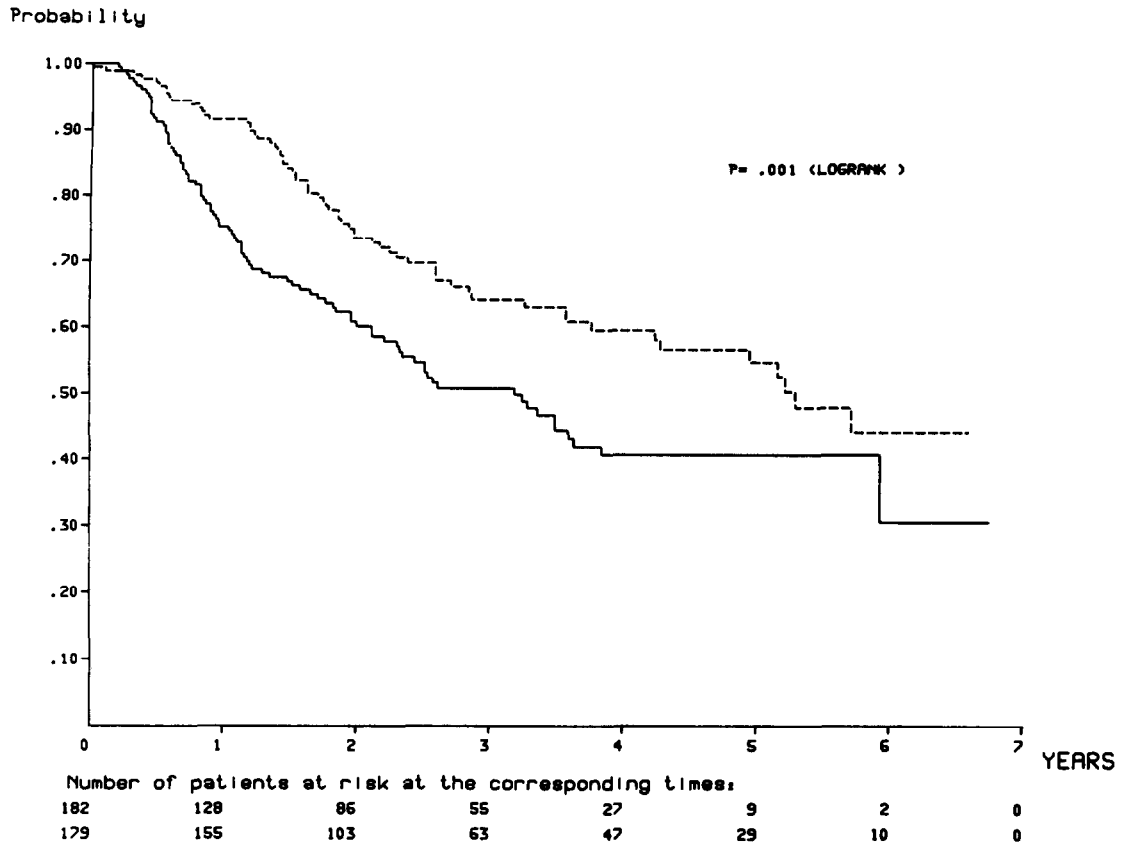


Fig. 6. Effect of chemotherapy on time to loco-regional progression (—— no chemotherapy;----- with chemotherapy).

Survival

Figure 9 shows the effects of the four different treatments on the duration of survival. A trend is seen in favour of the combination of hormone treatment and chemotherapy, but the difference between the four treatments is not statistically significant ($P = 0.12$). The individual effect of hormone treatment in extending survival just fails to reach significance ($P = 0.06$). The survival experience of pre- and postmenopausal patients was identical and similar results were obtained for the effects of the different treatments within these subgroups.

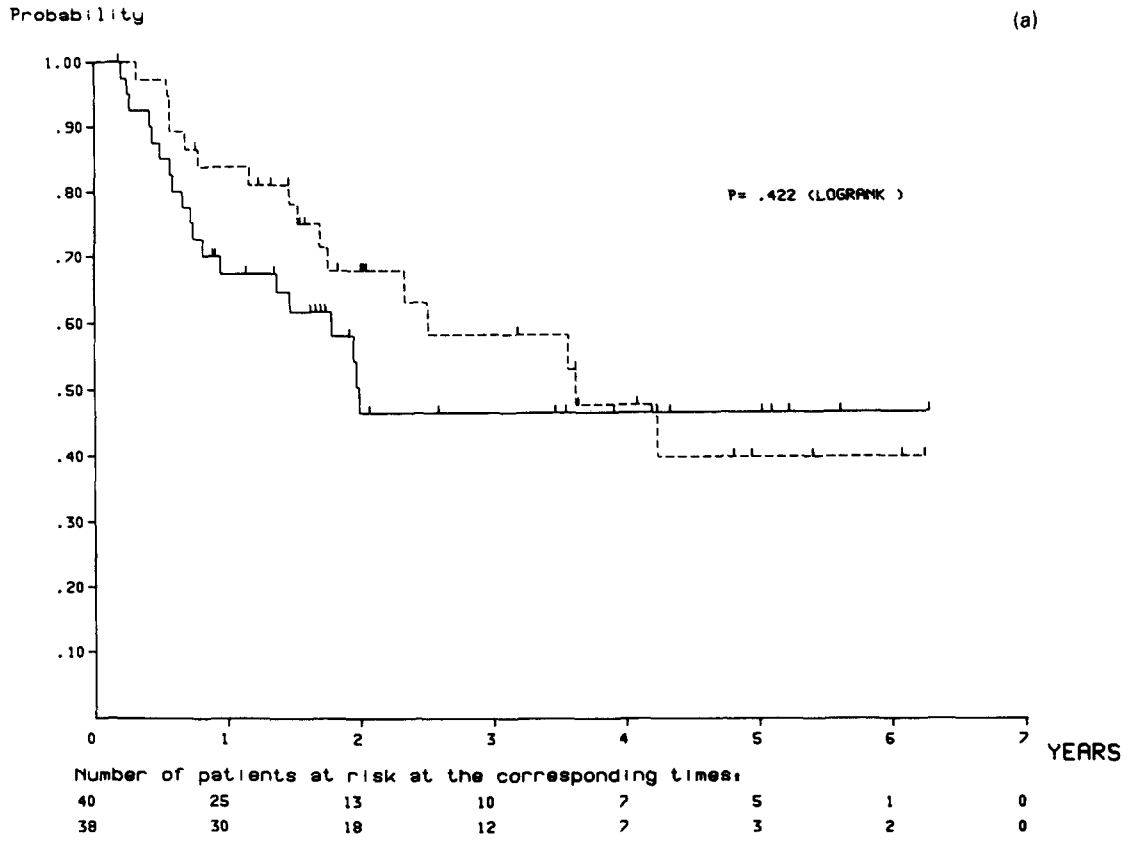
Age and menstrual status were neutral prognostic factors for survival, as were chest wall involvement and skin ulceration, but the following factors were associated with worse survival on univariate analyses with the log-rank test: skin oedema ($P = 0.0002$), skin nodules ($P = 0.007$), diffuse carcinoma ($P = 0.002$), inflammatory disease ($P = 0.0002$), axillary node involvement ($P = 0.02$), supraclavicular node involvement ($P = 0.002$) and oestrogen receptor level <10 fmol/mg cytosol protein ($P < 0.0001$). A detailed multivariate analysis will appear elsewhere.

Toxicity

Endocrine treatment, either ovarian ablation with prednisolone or tamoxifen, was essentially without adverse side-effects. Twenty-two per cent of patients so treated experienced hot flushes, but so did 10% treated by chemotherapy. Twelve cycles of chemotherapy were completed in 98/180 (54%) patients; reasons for earlier cessation included early death ($n = 5$), treatment refusal ($n = 23$), toxicity ($n = 2$) and disease progression ($n = 34$). Reductions in doses of cytotoxic drugs were recorded on one or more occasions in 91% of patients and treatment had to be delayed at least once in 48%. Haematological toxicity was moderate with haemoglobin falling below 9.5 g/dl in 18%, total white blood cell count to below 2×10^9/l in 8% and platelets to below 75×10^9/l in 18%. Only one episode of severe infection was noted. Nausea and vomiting was moderate in 34% of patients and severe in 12%. Stomatitis and diarrhoea were moderate to severe in 6% and 3% respectively; severe cystitis occurred in one patient. Alopecia developed in 41%. Disturbances in liver biochemistry were observed in 5% and in renal function in one patient.

DISCUSSION

The aim of combining systemic treatment with radiotherapy in the primary management of locally advanced breast cancer was to decrease and hopefully eliminate micrometastases present at the time of presentation. To this end, the results are disappointing. The effect of systemic treatment on time to distant metastases was minimal, although there



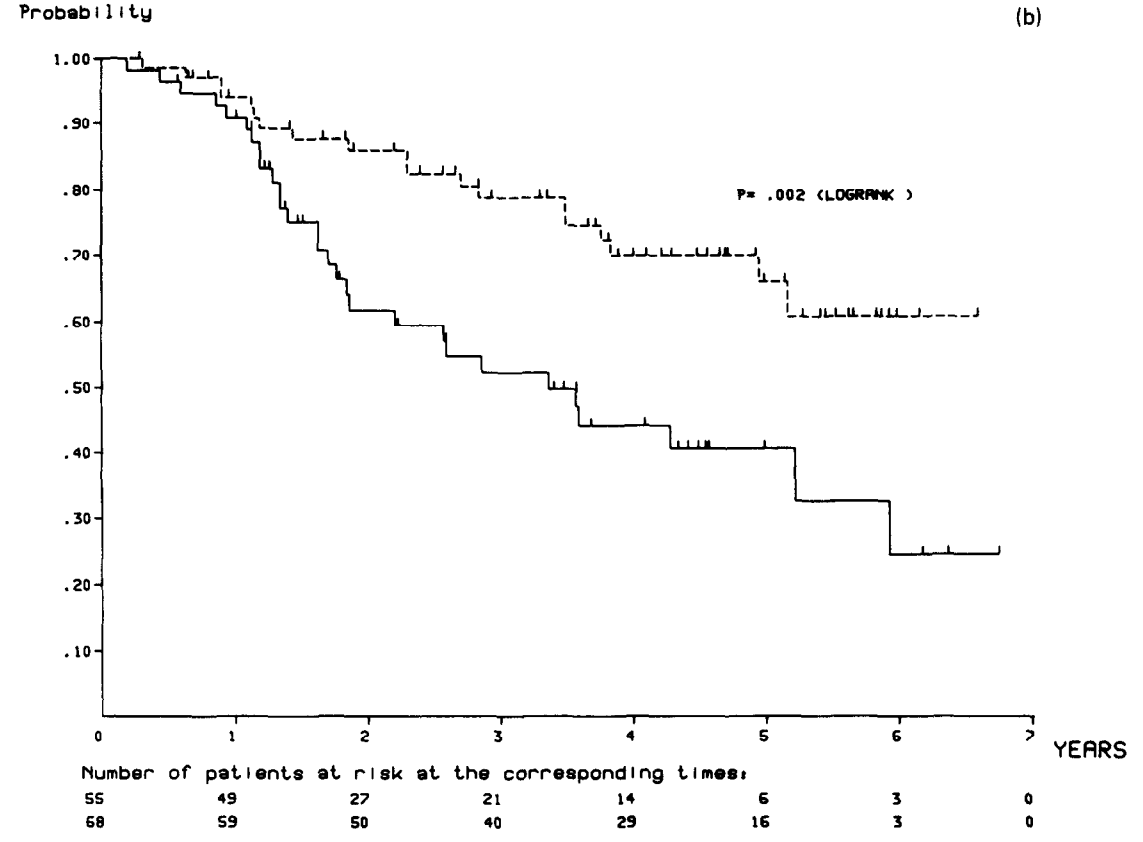


Fig. 7. Effect of endocrine therapy on time to loco-regional progression (—— no endocrine therapy; ----- with endocrine therapy) in (a) patients with oestrogen receptor negative (<10 fmol/mg cytosol protein) tumours; (b) patients with oestrogen receptor positive (≥10 fmol/mg cytosol protein) tumours.

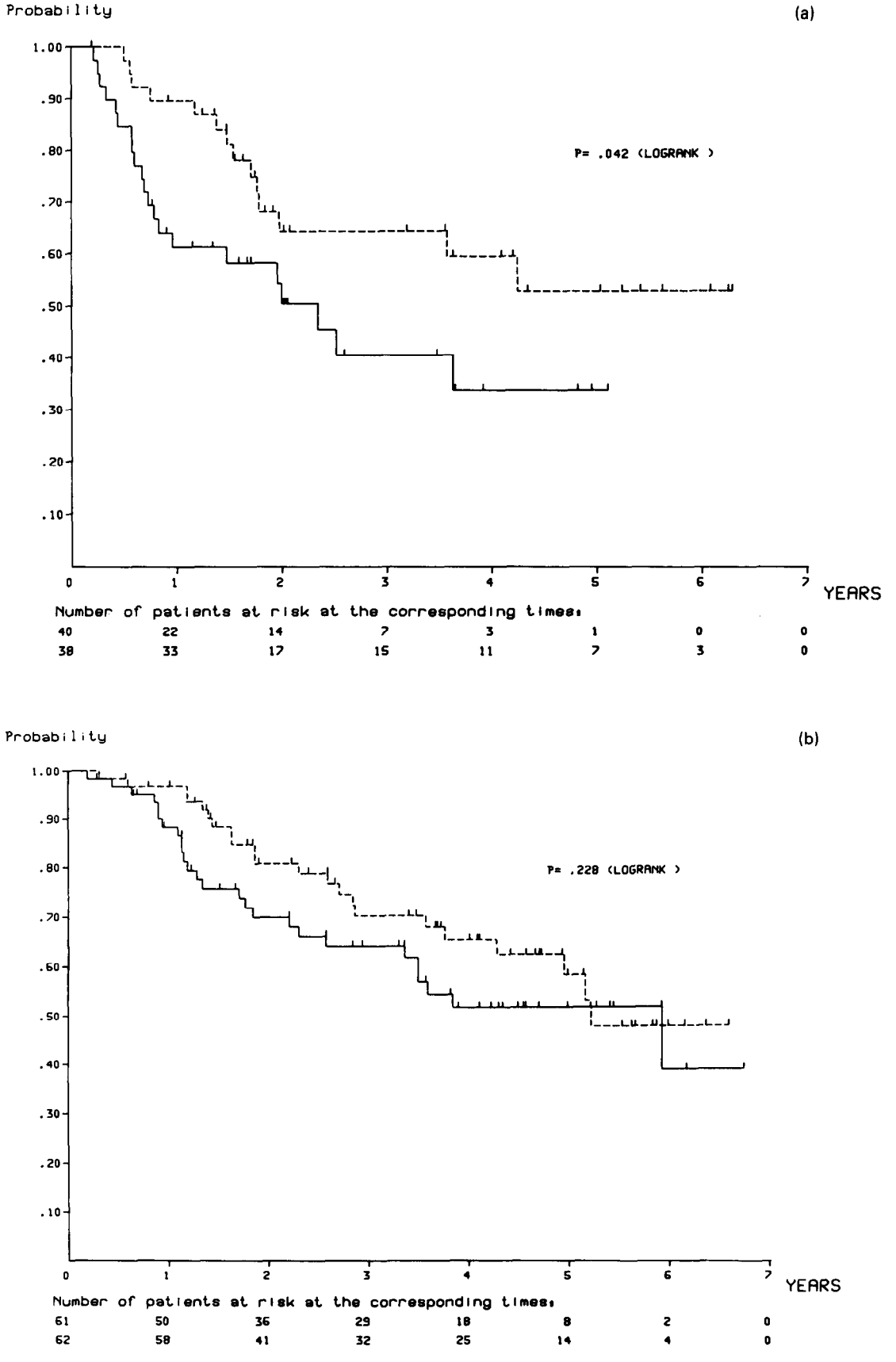


Fig. 8. Effect of chemotherapy on time to loco-regional progression (——— no chemotherapy; ----- with chemotherapy) in (a) patients with oestrogen receptor negative (<10 fmol/mg cytosol protein) tumours; (b) patients with oestrogen receptor positive (≥10 fmol/mg cytosol protein) tumours.

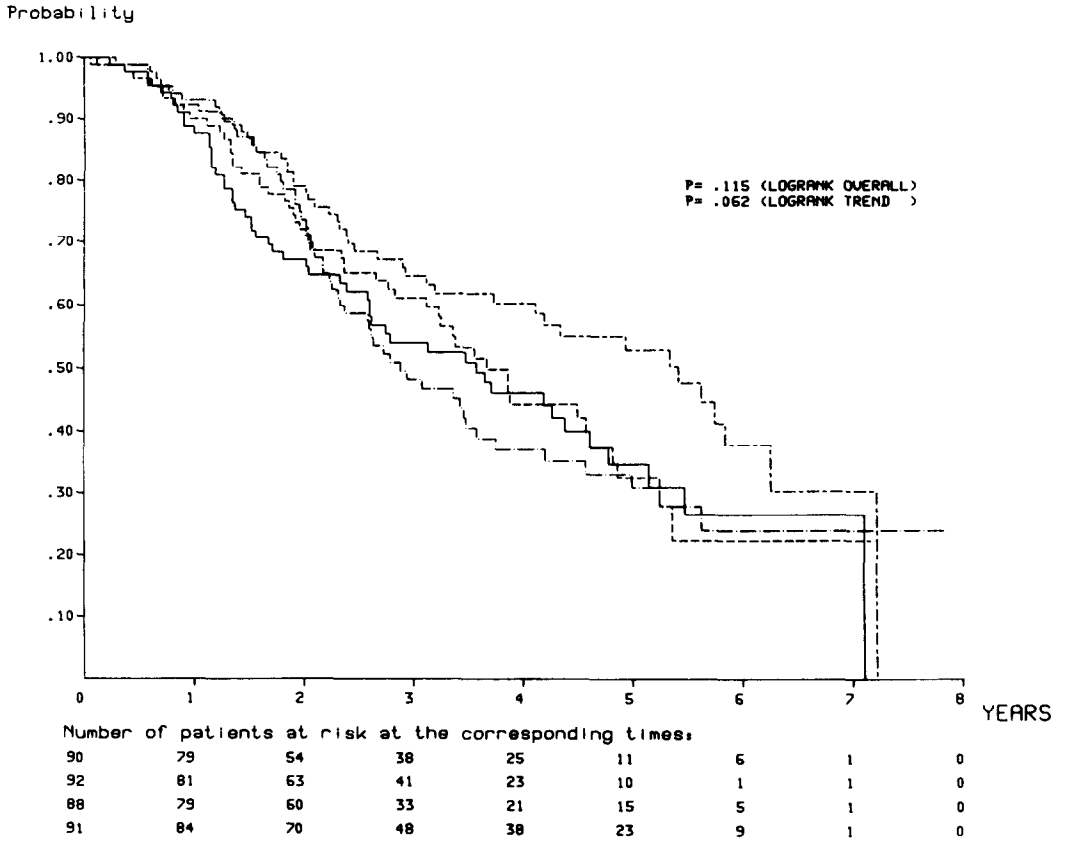


Fig. 9. Duration of survival (—— radiotherapy alone; ----- radiotherapy + endocrine therapy; -·-·- radiotherapy + chemotherapy; —·— radiotherapy + endocrine therapy + chemotherapy).

was a marginal effect on survival. Endocrine treatment and chemotherapy each had a major effect in improving control of loco-regional disease. The reason for this is uncertain. Possibly cells which metastasize could have an intrinsically lower sensitivity to systemic treatment than cells which remain localized. Alternatively, it is possible that local radiotherapy may have sensitized residual local cancer cells to subsequent systemic treatment. Mathematical modelling of the results from this trial has suggested that adjuvant systemic treatment reduces the burden of residual local cancer cells by an extra 100-fold after radiotherapy [11].

Control of local disease is undoubtedly important for patients' quality of life. Whether or not improvement in local control by systemic therapy achieves this end is not known from this study as it was not designed to assess the relative cost–benefits of treatment in relation to local control. This is an important question to be resolved as it is possible that local control could be improved further by higher radiation doses without systemic treatment [12]. Furthermore, the role of regional perfusion by cytotoxic drugs could be of value.

Notwithstanding the importance of local control, the main problem in locally advanced breast cancer leading to poor survival is the high incidence of distant metastases. To achieve better control of disseminated disease in patients presenting with this heterogeneous stage of breast cancer, much more work needs to be done. Several approaches can be considered and include earlier use of systemic treatment, high dose chemotherapy (possibly with autologous bone marrow transplantation), elucidation of the precise role of steroid receptors in the selection of treatment and methods to increase the chemosensitivity of tumour cells—oestrogen recruitment and sensitization by radiotherapy are possibilities. In the meantime, this trial suggests that current endocrine and cytotoxic treatments are only of marginal value in improving the prognosis in locally advanced breast cancer.

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