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Locally advanced primary breast cancer: medium-term results of a randomised trial of multimodal therapy versus initial hormone therapy

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Abstract

We report the medium-term (median follow-up = 52 months) results of a prospective randomised trial of multimodal therapy (neoadjuvant chemotherapy, Patey mastectomy, postoperative radiotherapy and adjuvant hormone therapy) ($n = 56$) versus initial hormone therapy ($n = 52$) for locally advanced primary breast cancer. Compared with multimodal therapy, initial hormone therapy was associated with reduced number of therapies for disease control (mean = 3.6 versus 4.9) and mastectomy rate (31%). Multimodal therapy conferred better initial locoregional control and a longer disease-free interval. Nevertheless, there was no statistically significant differences in the rates of survival, metastasis and uncontrolled locoregional disease, as well as in the time to metastasis between the two therapy groups. Regardless of the therapy groups, oestrogen receptor positivity conferred a lower metastasis rate, better survival and locoregional control. Thus, initial hormone therapy may be a reasonable option for managing locally advanced primary breast cancer, especially for oestrogen receptor-positive tumours.

Keywords: Locally advanced primary breast cancer; Multimodal therapy; Hormone therapy

1. Introduction

Locally advanced primary breast cancer (LAPC) is a heterogenous disease accounting for approximately 10–15% of all newly diagnosed breast cancers [1]. Locally advanced primary breast cancers usually comprise a combination of relatively indolent tumours in patients who have 'hidden' the lesion for years, rapidly growing cancers (often oestrogen receptor (ER)-negative in young women) and inflammatory breast cancers. Overall, patients with LAPC are at higher risk of local recurrence and distant metastases and therefore have a poorer survival outcome [2].

Unlike early primary breast cancer, surgery in the form of either breast conservation or mastectomy is often not a feasible treatment at least initially because of tumour size and involvement of the overlying skin and/or chest wall. Other modalities such as chemotherapy, radiotherapy and hormone therapy when used alone usually do not result in permanent local control.

The management of LAPC has evolved over the past few decades to the currently popular multimodal approach with neoadjuvant chemotherapy, surgery, radiotherapy and adjuvant hormone therapy, all given upfront. While this approach may improve initial local control, each of these modalities has associated morbidity and it is unclear whether all patients with LAPC will benefit from initial treatment with a combination of all these therapies, particularly given the heterogeneity of the tumours.

While there have been many trials evaluating various neoadjuvant chemotherapy regimes in the multimodal therapy for LAPC, trials designed to compare different therapeutic approaches are sparse. The Nottingham Breast Unit has conducted two randomised trials of this kind. The first was a cross-over trial comparing initial treatment with radiotherapy versus tamoxifen [3]. It

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showed no difference in terms of local disease control, metastases-free interval and survival between the two groups. The local control was comparable to a study conducted by Rubens and colleagues (1989) where LAPC was treated with combined radiotherapy and hormone therapy [4]. It would appear from this indirect comparison that sequential use of single treatment modalities gave almost identical duration of control compared with both treatments given together and did not compromise patient outcome. Such an approach may have an advantage over upfront multimodal therapy in that the morbidity of any unnecessary therapies could be reduced.

A subsequent randomised trial was carried out at Nottingham comparing initial hormone therapy with multimodal therapy consisting of neoadjuvant chemotherapy, Patey mastectomy, post-operative radiotherapy and adjuvant hormone therapy. At a median follow-up of 30 months, this trial showed no compromise in short-term outcome between the two groups [5]. The medium-term results at a median duration of 52 months of this trial are now presented.

2. Patients and methods

Between January 1989 and December 1994, patients with LAPC seen at the Nottingham Breast Unit who were considered fit to have chemotherapy and surgery were invited to enter the study. A total of 108 patients were recruited (Fig. 1).

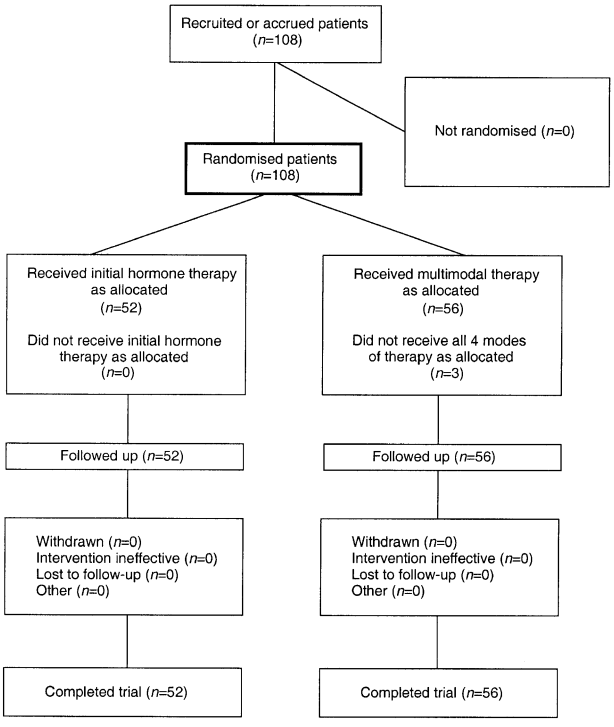

Fig. 1. Flow chart of the progress of patients through the trials (adapted from Ref. [18]).

LAPC was defined as histologically- or cytologically-proven, primary tumour $\geqslant 5$ cm, inflammatory breast cancer and/or with skin involvement, chest wall fixity or fixed axillary lymph node(s) at the time of diagnosis, in the absence of distant metastases as determined by investigations including full blood count, serum urea and electrolytes, liver function tests, chest radiograph and limited radiographic skeletal survey. Isotope bone scan and liver ultrasonography were done only if clinically or biochemically indicated.

In patients <55 years of age who had undergone hysterectomy or were within 2 years of their last menstrual period, their menopausal status was determined by serum luteinising hormone and follicular stimulating hormone levels.

All the patients were followed-up in a dedicated LAPC clinic and reviewed every 2 months for 6 months and every 3 months thereafter. The tumour size was assessed clinically using callipers. Blood tumour markers (CA15.3 and carcinoembryonic antigen (CEA)) were also done during each review. Re-staging investigations were carried out when there was a suspicion of metastases, either clinically or biochemically. Response to systemic therapy was assessed using the Union Internationale Contre le Cancer (UICC) criteria [6] and with adherence to the British Breast Group (1974) recommendation that a useful response should be of a minimum duration of six months [7]. Change in treatment was carried out at the time of progressive disease (PD). All patients were followed-up in this dedicated LAPC clinic until either death or their last clinic visit.

2.1. Trial protocol

The trial protocol was detailed in the previous publication and is therefore only summarised here. In the previously published early results of this trial [5], it was reported that 53 patients were randomised into the initial hormone therapy group, while 55 patients received the multimodal therapy. It was discovered during the analysis of the medium-term results that one patient who was previously analysed as in the initial hormone therapy group had actually received multimodal therapy. This was rectified in the present analysis.

2.1.1. Initial hormone therapy

52 patients were randomised to receive initial hormone therapy. Post-menopausal patients ($n=45$) had tamoxifen 20 mg daily, while pre-menopausal patients ($n=7$) received tamoxifen 20 mg daily and goserelin 3.6 mg as a subcutaneous (s.c.) injection monthly as the sole initial hormone therapy. The hormone therapy was continued until there was evidence of PD. When this happened, the most appropriate treatment (e.g. surgery, radiotherapy, chemotherapy) was given and the patient

followed-up until there was evidence of another PD, after which the, most appropriate treatment at that time was given. Hence the patient had only one modality of therapy at a time.

2.1.2. Multimodal therapy

56 patients were randomised to receive multimodal therapy. Neoadjuvant chemotherapy using the 'MMM' regime (mitoxantrone 7 mg/m^2 and methotrexate 30 mg/m^2 3-weekly for four cycles, mitomycin C 7 mg/m^2 3-weekly during the first and third cycles) was given to all patients. One patient withdrew after the first cycle for psychiatric reasons. She also refused surgery as well as radiotherapy. She was then started on megestrol acetate 160 mg twice daily. The tumour in 2 patients remained fixed to the chest wall after completing chemotherapy and therefore radiotherapy was given. These patients subsequently received hormone therapy.

All the remaining 53 patients underwent a Patey mastectomy, i.e. modified radical mastectomy (total mastectomy, resection of pectoralis minor plus full axillary clearance up to level III). All but 3 patients (due to contra-indication or patient refusal) had post-mastectomy flap irradiation, receiving 40 Gy in 15 fractions over 3 weeks (using 10 meV electron beams to the chest wall).

Adjuvant hormone therapy was given after mastectomy. Pre-menopausal patients ($n=10$) received tamoxifen 20 mg daily and goserelin 3.6 mg as a s.c. injection monthly, while those who were rendered post-menopausal by the neoadjuvant chemotherapy ($n=45$) had tamoxifen 20 mg daily only. The adjuvant hormone therapy was continued until there was evidence of locoregional failure or development of distant metastases, after which the most appropriate treatment was given.

2.2. Oestrogen receptor status

Patients were unselected for ER status. However, ER status was measured for the purpose of analysis and it was available in 103 patients. The H-score was determined by ER immunohistochemical assay (ERICA) [8]. Tumours were considered ER-positive when the H-score was $\geqslant 5$ and ER-negative when it was <5.

2.3. Locoregional failure

Locoregional failure was defined as PD in the breast or mastectomy flap and/or ipsilateral axilla according to UICC criteria. In other words, the first locoregional failure occurred in the initial hormone therapy group when the tumour progressed and/or recurrence developed in the ipsilateral axilla. In the multimodal therapy group, the first locoregional failure would be when recurrence developed in the mastectomy flap and/or the ipsilateral axilla.

2.4. Uncontrolled locoregional disease

Uncontrolled locoregional disease was defined as locoregional failure that had failed to respond to any treatment modality, i.e. all appropriate and available therapies have been used, but there was still no response.

The time to locoregional failure, time to metastases and survival were calculated from the commencement of the first therapy.

2.5. Statistical analysis

Statistical analysis was carried out using the standardised biomedical computer programme the Statistical Package for the Social Sciences (SPSS) for Windows (SPSS UK Ltd). Comparison of frequencies of integers between variables was using the Chi-squared test with Yates correction where appropriate. Differences in survival, time to metastases and time to locoregional failure between the groups were compared using the Wilcoxan (Gehan) statistics. With regards to this calculation, patients were followed independently, i.e. patients were not censored for one event because the other had occurred. The curves were censored at 84 months, as the number of patients beyond this time period was very small. A statistically significant difference was defined by $P<0.05$.

3. Results

Patient characteristics with respect to age, tumour size and length of follow-up in both groups were comparable (Table 1). In the multimodality group, the axillary lymph nodes were not involved in 2 (4%) patients, while 15 (27%) had one to three axillary nodes involved and 39 (70%) had four or more axillary nodes involved on histology of the axillary clearance.

3.1. Locoregional control

3.1.1. Initial response to therapy

At the end of 6 months, more than two-thirds of patients on the initial hormone therapy had an objective

Table 1
Patient characteristics

	Initial hormone therapy	Multimodal therapy
n	52	56
Median age (range) (years)	62 (36–73)	58 (32–71)
Mean tumour size (range) (cm)	6.2 (2.7–09.0)	6.5 (3.0–11.4)
Inflammatory carcinoma	6 (12%)	5 (9%)
T2 N2 tumour	12 (23%)	7 (13%)
T3 tumour	34 (64%)	44 (79%)
Median follow-up (range) (months)	45 (7–0113)	52 (6–120)

response (OR) (complete response (CR) and partial response (PR)) or stable disease (SD). However, almost all patients in the multimodal therapy group had an OR or SD after neoadjuvant chemotherapy (Table 2).

3.1.2. Medium-term response

Although more patients in the initial hormone therapy group ($n=41$) developed PD when compared with patients in the multimodal therapy group ($n=11$), the rates of uncontrolled locoregional disease were similar in both groups ($n=3$ and $n=2$, respectively).

The time to first locoregional failure was significantly shorter in the initial hormone therapy group when compared with the multimodal therapy group ($P<0.01$) (Fig. 2).

3.2. Systemic control

There was no difference in the number of patients who developed distant metastases ($n=29$ and $n=30$ for those treated with initial hormone therapy and multimodal therapy, respectively), as well as in the time to distant metastases between the two groups (Fig. 3).

No significant difference was seen in the number of breast cancer-related deaths (Table 3), as well as the overall survival (Fig. 4) between the two groups.

Table 2
Initial response

	Initial hormone therapy *n* (%)	Multimodal therapy *n* (%)
Complete response	2 (4)	5 (9)
Partial response	17 (33)	26 (47)
Stable disease	16 (31)	22 (40)
Progressive disease	17 (33)	2 (4)

3.3. Number of therapies

When compared with the multimodal therapy group, patients in the initial hormone therapy required less therapies to achieve disease control (Table 4).

16 patients (31%) in the initial hormone therapy group eventually underwent mastectomy for locoregional control of their tumour, although over 80% required a 'local' therapy (i.e. either surgery (31%) or radiotherapy (52%)).

Table 3
Survival status by treatment groups

	Initial hormone therapy *n* (%)	Multimodal therapy *n* (%)	*P* value
Alive	15 (29)	25 (45)	
Dead from breast cancer	35 (67)	29 (52)	0.23
Dead from other causes	2 (4)	2 (4)	

Table 4
Number of different therapies required for locoregional and systemic control

No. of different therapies	Initial hormone therapy (*n*)	Multimodal therapy (*n*)
1	7	0
2	7	0
3	8	0
4	15	33
5	9	7
6	5	8
7	1	3
8	0	4
9	0	1
Total no of therapies	187	277
Mean	3.6	4.9

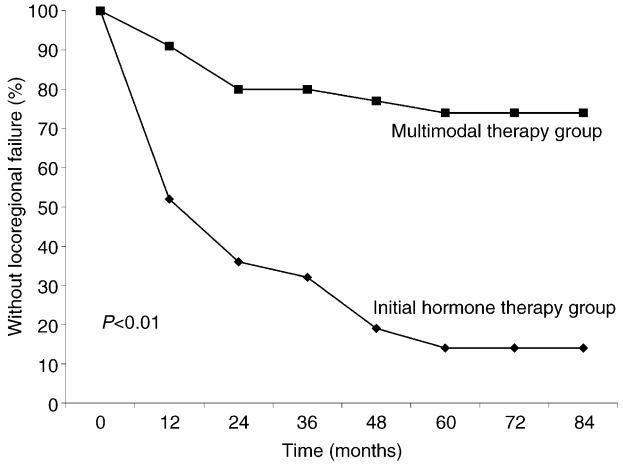

Fig. 2. Time to development of first locoregional failure by treatment groups.

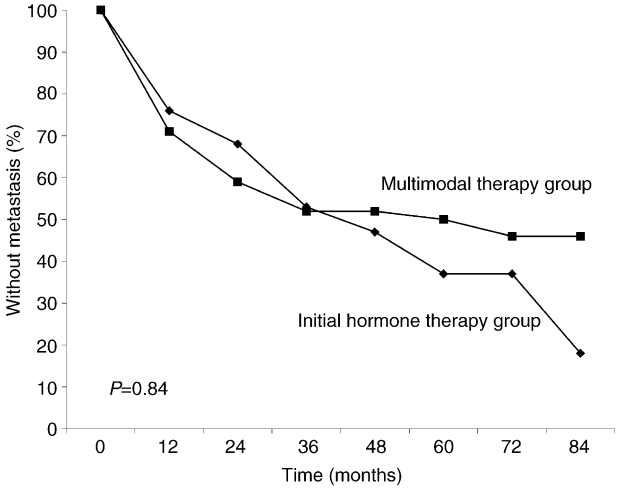

Fig. 3. Time to development of distant metastasis by treatment groups.

3.4. Analysis according to oestrogen receptor status

There were slightly more ER-positive tumours in the initial hormone therapy group ($n=35$) compared with the multimodal therapy group ($n=28$), but this was not statistically significant ($P=0.09$).

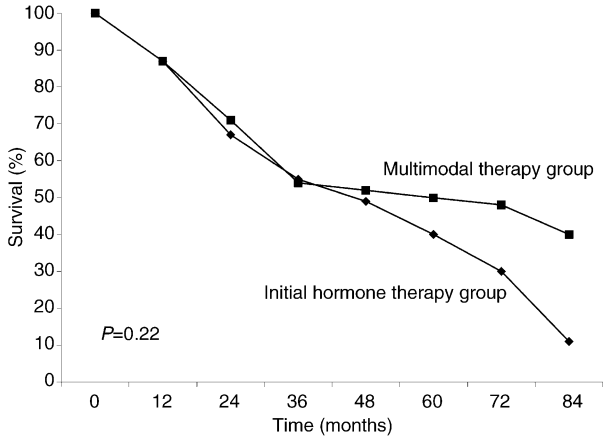

Fig. 4. Overall survival by treatment groups.

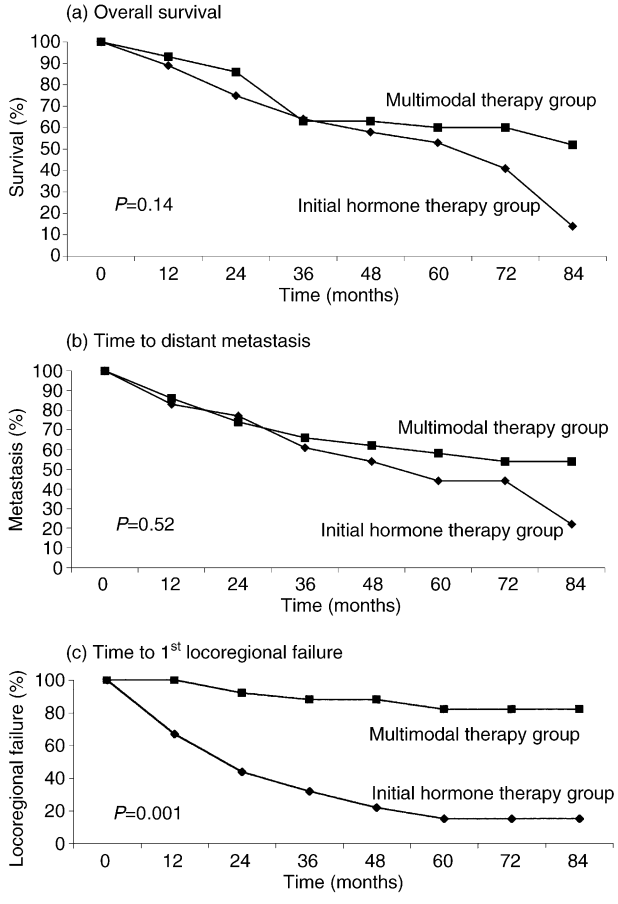

Fig. 5. (a) Overall survival by treatment groups in ER-positive tumours. ER, oestrogen receptor. (b) Time to development of distant metastases by treatment groups in ER-positive tumours. (c) Time to development of first locoregional failure groups in ER-positive tumours.

5 (36%) patients with ER-negative tumours who received initial hormone therapy had an OR or SD after 6 months of treatment (Table 5). These 5 patients developed PD after a median time of 16 months (range 8–27 months). 2 were given second-line hormone therapy resulting in PRs for 11 and 20 months, respectively. One underwent mastectomy and the remaining two patients were lost to follow-up.

Consistent with established findings, patients with ER-positive tumours did significantly better in terms of survival, time to locoregional failure and time to metastases in both the initial hormone therapy group and the multimodal therapy group (data not shown).

Table 5
Initial response in Initial hormone group according to ER status[a]

Response	ER-positive *n* (%)	ER-negative *n* (%)
Complete response	2 (6)	0 (0)
Partial response	15 (43)	1(7)
Stable disease	11 (31)	4 (29)
Progressive disease	7 (20)	9 (64)

ER, oestrogen receptor.
[a] ER status was unknown for 3 cases.

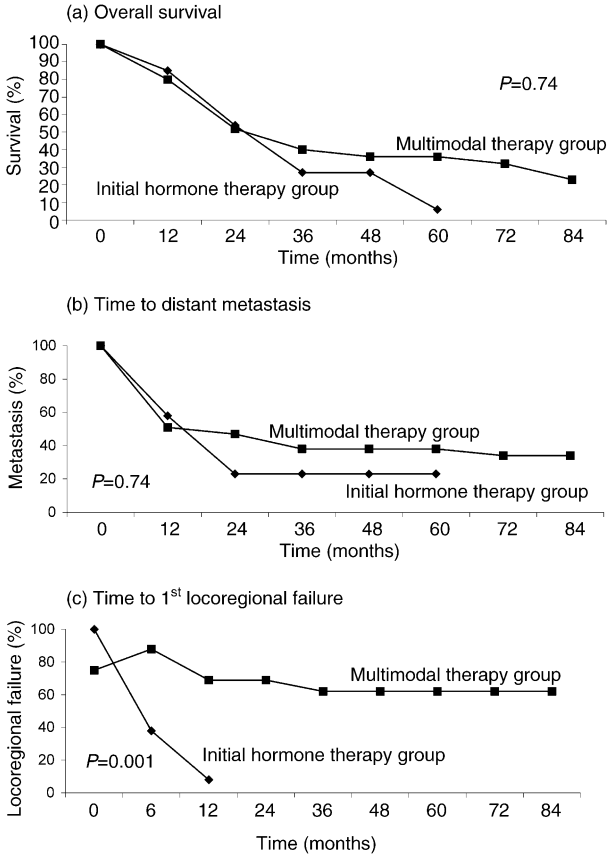

Fig. 6. (a) Overall survival by treatment groups in ER-negative tumours. (b). Time to development of distant metastases by treatment groups in ER-negative tumours.

Subgroup analysis showed no difference in survival and time to distant metastases between the two treatment groups regardless of the ER status (Figs. 5 and 6). The same pattern as in the overall analysis of all patients was also seen in the time to first locoregional failure in both groups regardless of the ER status.

4. Discussion

The management of LAPC is a continuing challenge to clinicians. The difficulties are high local recurrence rates and poor survival outcome due to metastatic disease [2]. In an attempt to overcome these problems, the management has evolved over the last three decades to the multimodal approach involving at least three to four different therapies all given upfront.

As noted above, LAPCs encompass a wide spectrum of disease ranging from the slow growing tumours to the aggressive inflammatory breast cancer [9]. With widely different clinical and biological characteristics, response to treatment varies considerably suggesting that some patients may not require the multimodal approach. The effectiveness of a management approach is determined by how good the locoregional as well as systemic control is.

In this trial which started in 1989, the MMM chemotherapy regimen was used. It was well tolerated and resulted in an OR rate of 56%. This was similar to that reported by Gazet [10] (53%) and Smith [11] (69%) who used the MMM chemotherapy regimen. The MMM chemotherapy regimen was acceptable and appropriate at the time this trial was commenced. The optimal duration of neoadjuvant chemotherapy remains undefined. A balance has to be sought between an unwanted delay of surgery and obtaining the best achievable response. In our experience with the MMM regime, most patients achieved the best response after four cycles. We recognise that newer regimes (e.g. an anthracycline-based one which we currently use) may result in more ORs, although the relevance of this in terms of time to recurrence post-surgery or overall survival has not been fully established. Patients in the initial hormone therapy group had a 35% OR rate which was comparable to those reported by others [12,13]. While neoadjuvant chemotherapy is more rapid in achieving a response compared with initial hormone therapy, it is unclear whether rapidity in response is important in terms of long-term locoregional control, metastases-free survival and overall survival.

The time to first locoregional failure was significantly shorter in the initial hormone therapy group compared with the multimodal therapy group. Similarly, the proportion of patients in the initial hormone therapy group who developed PD was much higher compared with those who developed locoregional recurrence in the multimodal therapy group. These were not equivalent comparisons as the patients in the multimodal therapy group had received all four therapies in combination for locoregional control, while the initial hormone therapy group had had only one modality when PD developed. Another way of assessing long-term locoregional control is to look at the number of uncontrolled diseases and this was similar in the two treatment groups.

Although patients with LAPC treated with initial hormone therapy had earlier locoregional failure, this was salvaged and brought under control with further therapy. However, over 80% required some form of local therapy (surgery 31%, radiotherapy 52%) and it could be argued that perhaps hormone therapy might be combined with local treatment(s) initially. Only approximately a quarter of the patients who had initial hormone therapy subsequently required chemotherapy. The overall number of therapies needed was less than that required in the multimodal therapy group (Table 4). Ahern [14] conducted a trial in which patients with LAPC were treated with chemotherapy and radiotherapy and concluded that in a large number of patients, local control may be achieved using chemotherapy (i.e. a systemic therapy) and radiotherapy (i.e. a local therapy).

Systemic control of occult metastatic disease (i.e. time to metastases) was comparable between the two groups. There was no significant difference in the rate of metastases and time to distant metastases (Fig. 3). There are recent publications on primary breast cancer (including stage II and III tumours) suggesting that improved local control as a result of post-operative radiotherapy may not only reduce local recurrence, but also produce a moderate (i.e. 2–4%) increase in survival (data not shown). This present study does not have sufficient power to detect differences of this degree.

There was no significant difference in survival between the two groups of patients. The survival curves appear to separate over the last third of the follow-up period, but it should be emphasised that a number of patients drop off with each 3-month time period. However, at the end of the current follow-up period, there were more patients in the multimodal therapy group who were alive compared with the initial hormone therapy group (Table 3) although the difference was not statistically significant. Delayed separation of the survival curves is often difficult to interpret as the number of patients at risk decreases over the later time period. A similar separation at around 4 years has recently been reported in two studies of primary operable breast cancer in elderly patients that compared tamoxifen versus surgery plus tamoxifen [15]. All such studies have raised the question as to whether in a minority of patients delay in removing the primary tumour may allow the cancer to develop occult metastases which subsequently may impact on survival. Further survival analysis after longer follow-up is clearly warranted. However, at a

median follow-up of 52 months with 63% of patients having died, there is no statistically significant difference between the two treatment groups.

From the medium-term results of this trial, initial treatment of LAPC by sole hormone therapy showed no significant difference when compared with multimodal therapy except for initial locoregional control. Time to metastases and overall survival were not statistically different in the two groups, although at the end of the current follow-up period there were more patients alive in the multimodal therapy group compared with the initial hormone therapy group. These non-significant differences require further follow-up, but from what has been demonstrated in the initial hormone therapy group, not all of these patients, would have required all modalities of therapy for disease control.

However, patients treated with initial hormone therapy have to put up with experiencing multiple episodes of locoregional failure. Some patients may find this psychologically distressing even though the tumour can be controlled with a change of therapy and long-term outcome is unchanged. For this reason, where initial surgery is feasible, combining local treatment (surgery and/or radiotherapy) with systemic therapy may be an option that both patients and clinicians consider appropriate. However, multimodal therapy offers a long disease-free interval, but with the price of undergoing chemotherapy, radiotherapy and mastectomy together with their combined side-effects.

The potential of ER status to predict response to hormone therapy in LAPC has been reported [13]. In the current study, patients with ER-positive tumours did better than those with ER-negative tumours in the initial hormone therapy group. This was expected, but interestingly, the outcome for patients with ER-negative tumours did not improve significantly with multimodal therapy. Looking at the time to metastases curve (Fig. 6) this may be, in part, because most patients developed symptomatic metastases at 12–18 months, suggesting that they already had occult metastases at the time of initial presentation.

Patients with ER-positive tumours did better regardless of the treatment group in terms of median survival, time to metastases and time to locoregional failure. This may be due to the fact that both groups received hormone therapy either as an initial treatment or as adjuvant therapy. Similar results were reported by Kantarjian [16] who observed a longer disease-free interval in ER-positive LAPC treated with multimodal therapy and improved survival was also demonstrated by De Matteis [17] in ER-positive LAPC patients given multimodal treatment.

5 (36%) patients with ER-negative tumours who received initial hormone therapy had an initial PR or SD. This higher than usual response rate for ER-negative tumours may be due to non-representative sampling. Being a heterogeneously expressed antigen, the ER protein may be lost in the necrotic centre of a large tumour resulting in a false-negative result. Two of these patients had a subsequent PR to second-line hormone therapy suggesting that the tumours were hormone-sensitive and might in fact have been ER-positive.

In the overall analysis, there was no significant difference in outcome between the two therapeutic approaches, but in the subgroup analysis, patients in the initial hormone therapy group who had ER-positive tumours did better compared with those with ER-negative tumours. It would appear that from the current study, a sequential approach starting with hormone therapy especially in ER-positive tumours could achieve comparable long-term disease control with a lower number of treatment therapies, thus possibly avoiding some unnecessary treatments and their associated morbidity. However, it is theoretically possible that a subgroup of patients with ER-positive LAPC (probably those with T3N0 disease) might be cured by the multimodality approach. We would point out that only two patients in this group were found to be node-negative at modified radical mastectomy, although we also acknowledge that the staging was made after neoadjuvant MMM chemotherapy.

Finally, as this current trial was commenced in 1989, we recognised the statistical limitations of the trial. Firstly, the trial was commenced as a single centre study and the number of patients required to give adequate statistical power in calculating the events was not determined prospectively. By the same token, the number of patients in each arm was small to begin with and with dwindling number of patients as they die, the analysis of late events was limited. Such limitations were also seen and recognised when the subgroup analyses were carried out (Figs. 5 and 6). Nonetheless, there are few randomised trials of LAPC and this trial is one of the largest, especially looking at multimodality treatment.

Management of this unique group of patients with LAPC should be individually tailored according to tumour progression, individual response and the psychological profile of the patient. Sequential therapy starting with hormone therapy appears a reasonable option for the management of selected patients with ER-positive tumours, while the multimodal approach may be used for those with ER-negative tumours.

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