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# Factors Influencing Local Relapse and Survival and Results of Salvage Treatment after Breast-conserving Therapy in Operable Breast Cancer: EORTC Trial 10801, Breast Conservation Compared with Mastectomy in TNM Stage I and II Breast Cancer

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**A (modified) radical mastectomy (RM) was compared with breast-conserving therapy (BCT) in stage I and stage II breast cancer patients. Treatment of the study arm comprised lumpectomy, axillary clearance and radiotherapy to the breast (50 Gy in 5 weeks external irradiation and a boost with iridium implant of 25 Gy). 902 patients were included. There were 734 TNM stage II patients. Patients with microscopically incomplete excision of the tumour were not excluded. After a median follow-up of 6 years, overall survival and local recurrence rates do not differ significantly between the two study arms. Actuarial survival at 8 years was 73% after RM and 71% after BCT; actuarial local recurrence at 8 years was 9% and 15%, respectively. In the mastectomy group tumour size did not affect local relapse, but after BCT the incidence of local recurrences was higher for tumours of 2–5 cm (16%) than for smaller tumours (7%) (at 8 years, $P = 0.08$). Results of salvage treatment for local recurrence so far were similar in both the BCT and the mastectomy group.**
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## INTRODUCTION

BREAST CONSERVATION in the treatment of early breast cancer, using radiotherapy after local excision instead of complete removal of all breast tissue, was advocated by the pioneers Keynes [1] and Mustakallio [2] as early as the 1920s. However, their treatment approach was strongly challenged over the years and only since convincing data have emerged from randomised studies has this approach found a place in the standard treatment of operable disease [3–6]. Since most prospective studies were restricted to the TNM stage I situation only, the EORTC Breast Cancer Cooperative Group started in 1980 a study to evaluate the possibility of breast-conserving therapy (BCT) in operable breast cancer with the specific aim of looking at the results of BCT in patients with TNM stage II disease.

This report is based on the evaluation of April 1991, providing data of patients with a maximum follow-up of 10 years (median 6).

## PATIENTS AND METHODS

A (modified) radical mastectomy (RM) was compared with BCT, comprising lumpectomy with an attempted margin of 1 cm of healthy tissue and complete axillary clearance usually by a separate incision, followed by radiotherapy directed to the breast (50 Gy in 5 weeks) with an additional booster dose of 25 Gy directed to the lumpectomy site, using an $^{192}$iridium implant. In the rare cases where an implant was impossible for technical reasons an equivalent boost dose was given with external irradiation.

Some minor interinstitutional differences in relation to adjuvant chemotherapy and adjuvant parasternal radiotherapy were not considered relevant since indications in each centre were consistent during the trial period for the two study arms and the randomisation was stratified by centre. The participating centres were: Guy's Hospital, London ($n$ = 420), The Netherlands Cancer Institute, Amsterdam ($n$ = 201), University Hospital, Leuven ($n$ = 108), Tygerberg Breast Unit, Stellenbosch, S.A. ($n$ = 80), Radiotherapy Institute, Rotterdam ($n$ = 51), three other hospitals together (St. Lucas Hospital, Amsterdam, The Maria Hospital, Tilburg and St. Jans Hospital, Brugge) ($n$ = 42). Data collection and analysis were performed in the EORTC Data Centre, Brussels. Some centres participated only in the later years of trial intake. The majority of the centres participated only for TNM stage II patients; Guy's Hospital entered the majority of the TNM stage I patients. The trial was closed to entry in 1986.

Patients were stratified by participating centre, stage (I and II) and menopausal status. The randomisation was performed centrally in the EORTC Data Centre in Brussels.

Excluded were patients 71 years of age and older, patients with a Karnofsky index below 80%, patients with tumours fixed to the muscles, or with other questionable operability, with multicentric tumours and with large tumours in small breasts.

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*Table 1. Yearly intake of patients in the study*

| | |
|---|---|
| 1980 | 24 |
| 1981 | 78 |
| 1982 | 184 |
| 1983 | 176 |
| 1984 | 196 |
| 1985 | 189 |
| 1986 | 55 |
| | 902 |

Exclusion criteria included a previous history of other malignancies apart from basal cell carcinoma of the skin and *in situ* carcinoma of the cervix uteri, inability to conform to strict follow-up, being emotionally or psychologically unfit to undergo BCT and (optional) positive axillary apex biopsy. Patients were not excluded if at the pathology investigation it was found that the excision had been microscopically incomplete. Re-excisions only rarely were performed.

End-points were survival, local control, time to distant metastasis and quality of life.

All relapses within the treated area (breast or thoracic wall and axilla) were considered to be local failures, including new tumours and those local recurrences appearing before, together with, or after the manifestation of distant disease. Supraclavicular metastases were not considered as local recurrences.

All patients were followed up according to a standard regimen. Quality of life was evaluated by standard questionnaires at 2 and at 4 years, allowing insight into body image, fear of recurrence and satisfaction with treatment. More detailed investigations, such as structured interviews were performed in some participating centres. Cosmetic outcome for the patients with BCT was judged by the doctor and patient on a four-point scale every year and also by independent panels, using standard photographs in three positions taken at 2 and at 4 years [7].

902 patients were entered of whom 734 (81%) had stage II disease (T1N0-1a, 168; T1N1b, 26; T2N0-1a, 565; T2N1b, 143). The majority of these patients were designated stage II because of clinical tumour size over 2 cm. The intake per year is given in Table 1. 9 patients were treated with BCT after having been randomised for mastectomy; 14 patients were treated with mastectomy after having been randomised for BCT. In the statistical analysis of the data the patient remained in the original treatment arm to which they had been assigned, regardless of the actual treatment performed. 21 patients were considered to be ineligible on review (equally distributed between both study arms) the main reasons being a too advanced tumour situation or an incorrect diagnosis.

In the first 2 years a 2:1 randomisation was performed since it was planned to share the control arm (mastectomy) with another European study. The numbers were adjusted during the further randomisation after 1982 to almost equal groups, reaching ultimately 425 eligible patients in the RM group and 456 eligible patients in the BCT group, giving a total of 881 eligible patients. For 2 eligible patients no follow-up data are available. Analysis of data confirmed that both groups were well balanced as shown in Table 2. The number of axillary nodes removed was equal for the patients in both groups (in 50% of the cases of both study arms the number of nodes examined was 18 or more) indicating comparable techniques in relation to completeness of the axillary surgery in both study groups.

Endpoints of duration of survival, time to distant metastases and time to local recurrence were measured from randomisation. They were censored at the last follow-up time. Patients were still followed-up for local recurrence after distant metastases and vice versa. Survival curves were calculated using the Kaplan–Meier technique. The logrank test was used to assess the significance of patients' characteristics as prognostic factors and to compare efficacy of treatments. Where appropriate, trend tests were performed using a logrank test for trend. Adjustment of treatment comparisons for important prognostic factors was performed by using a stratified logrank test [8].

## RESULTS

The curves indicating overall survival, time to distant metastases and time to local regional recurrence (excluding supraclavicular) are virtually superimposable for both groups (Figs 1, 2 and 3). The total number of thoracic wall recurrences in the mastectomy group was 35 (8%). In the BCT group there were 47 (10%) recurrences within the treated breast, of which 8 were combined with axillary recurrences. Another 5 cases developed isolated axillary recurrences. The relation between local and distant recurrence is given in Table 3. The actuarial 8 year local control rate (S.E.) was 91(2)% (standard error) in the radical mastectomy group and 85(2)% in the BCT group. The difference in time to local recurrence was not statistically significant. In Fig. 4 the curves indicating local recurrence rates are given separately for patients with tumours up to and including 2 cm and those over 2 cm (clinical measurement). For the mastectomy patients the local recurrence rates were equal for the patients with smaller and larger tumours [actuarial local relapse rate at 8 years, 8(3)%], whereas in the BCT arm the actuarial local relapse rate at 8 years was 16(3)% for the patients with tumours larger than 2 cm and only 7(3)% for those with smaller tumours (logrank $P = 0.08$).

*Table 2. Balance in patients' and tumour characteristics*

| | | M (%) | BCT (%) |
|---|---|---|---|
| Age | < 50 years | 35 | 37 |
| | 50–59 years | 36 | 31 |
| | 60+ years | 28 | 32 |
| Menopausal status* | premenopausal | 39 | 49 |
| | postmenopausal | 52 | 54 |
| | artificial postmenopausal | 6 | 4 |
| Stage | clin. TNM stage I | 18 | 17 |
| | clin. TNM stage II | 81 | 83 |
| T stage | clin. T1 | 21 | 20 |
| | clin. T2 | 79 | 79 |
| pT stage* | pT1 (< 2 cm) | 38 | 38 |
| | pT2 (2–5 cm) | 57 | 58 |
| N stage* | clin. N0 | 71 | 68 |
| | clin. N1a | 9 | 9 |
| | clin. N1b | 17 | 19 |
| pN stage* | N− | 56 | 53 |
| | N+ | 39 | 43 |
| No. pos. nodes | 1 | 16 | 21 |
| | 2–3 | 8 | 11 |
| | 4–9 | 10 | 6 |
| | 10+ | 5 | 4 |
| Adj. chemother. (N+ cases) | no | 62 | 57 |
| | yes | 38 | 43 |

* Figures do not necessarily add completely to 100% due to missing data.

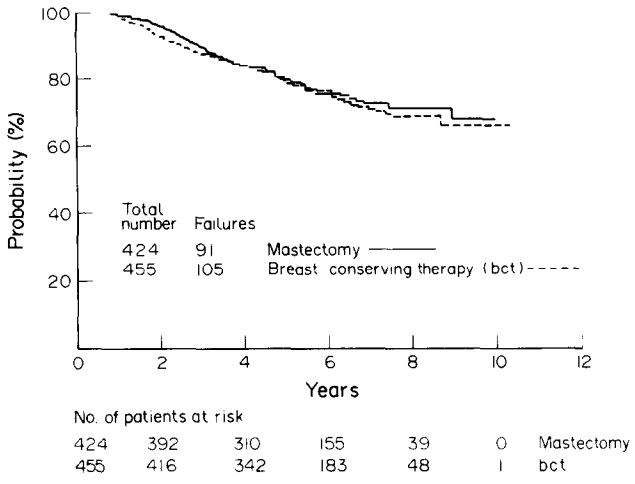


**Fig. 1. Duration of survival after breast-conserving therapy and radical mastectomy in stage I and II breast cancer. Logrank $P$ = 0.71.**

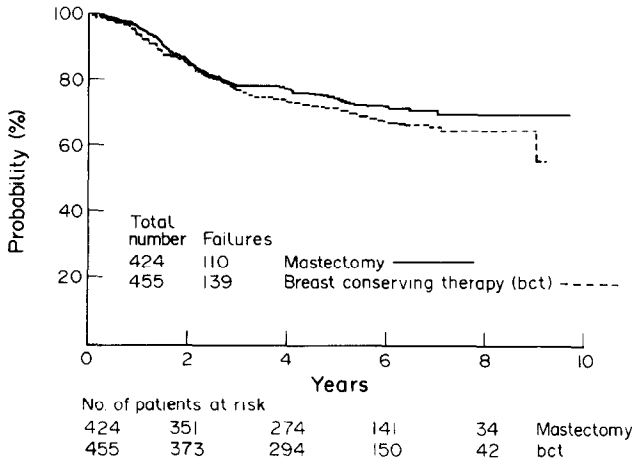


**Fig. 2. Time to distant metastases after breast-conserving therapy and radical mastectomy in stage I and II breast cancer. Logrank $P$ = 0.19.**

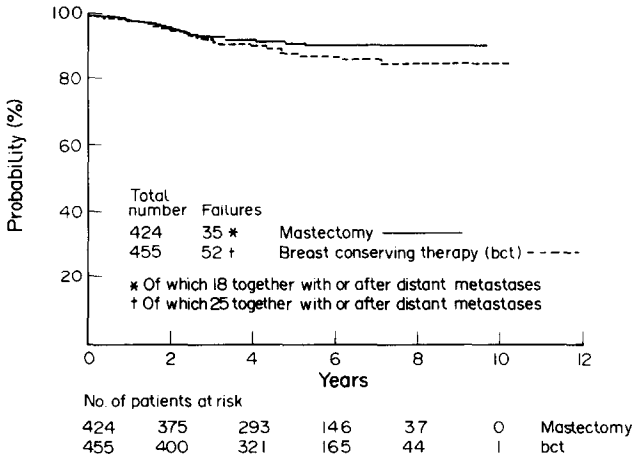


**Fig. 3. Time to local recurrence after breast-conserving therapy and radical mastectomy in stage I and stage II breast cancer. Included are also patients with new tumours in the ipsilateral breast and those recurrences appearing before together with or after distant metastasis. Logrank $P$ = 0.14.**

*Table 3. Sites of recurrence*

| | No recurrence | Local only or local before distant | Local together with distant | Local after distant | Distant only | Total |
|---|---|---|---|---|---|---|
| RM | 296 | 17 | 12 | 6 | 93 | 424 |
| BCT | 292 | 27 | 23 | 2 | 111 | 455 |
| | 588 | 44 | 35 | 8 | 204 | 879 |

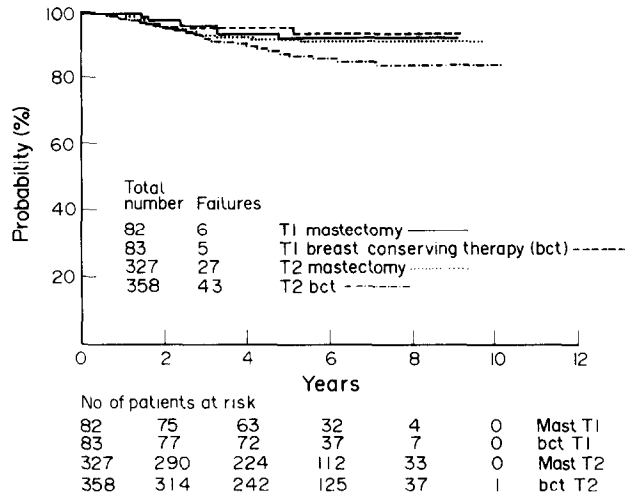


**Fig. 4. Time to local recurrence in the two study arms split up in smaller and larger tumours. Logrank $P$ = 0.15 (overall), Logrank $P$ = 0.08 T1 versus T2 bct, Logrank $P$ = 0.71 T1 versus T2 mastectomy.**

Figure 5 shows curves of node-negative (N−) and node-positive (N+) patients in both treatment groups. The influence of nodal status on local recurrence, which is significant for all patients of both study arms together (logrank $P$ = 0.001) again is more pronounced in the BCT group than in the RM group. This prognostic effect was less apparent in the BCT patients treated with adjuvant therapy with 15(4)% actuarial 8 year local relapse rate in the BCT N+ patients, who were treated with

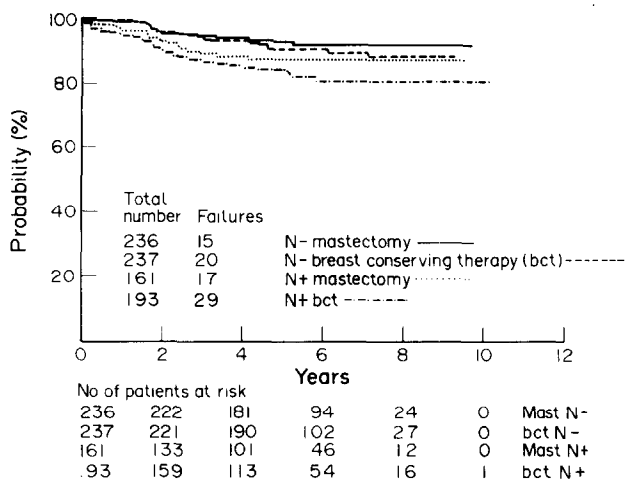


**Fig. 5. Time to local recurrence in the two study arms split up in N− and N+ cases. Logrank $P$ = 0.004 (overall).**

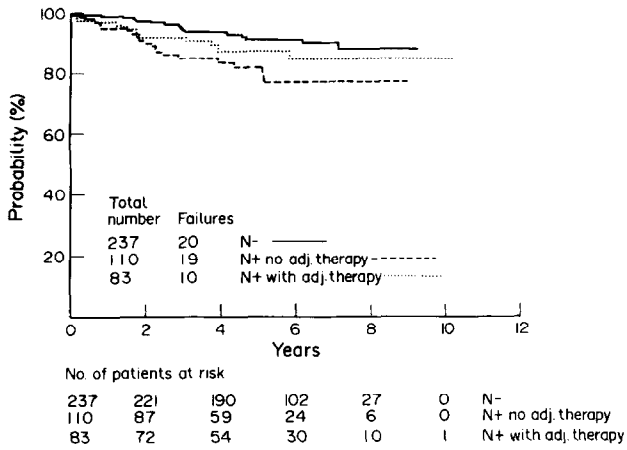


**Fig. 6. Time to local recurrence in the BCT cases, split up in node negative patients and node positive cases with or without adjuvant chemotherapy. Logrank $P = 0.009$ (overall).**

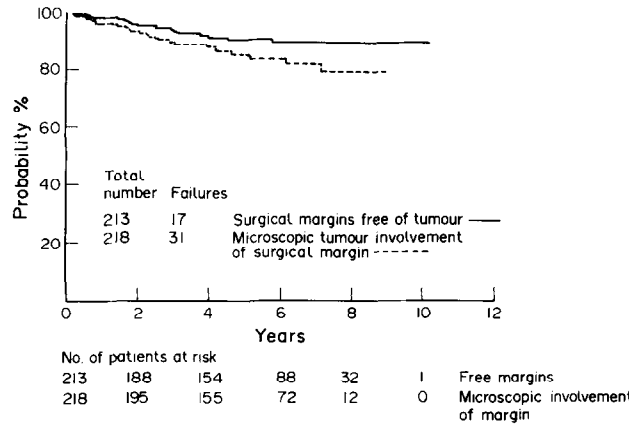


**Fig. 8. Time to local recurrence in the BCT cases split up in cases who were completely excised and those who had microscopic involvement of margins. Logrank $P = 0.10$ (overall), logrank $P = 0.15$ (trend).**

adjuvant chemotherapy versus 23(5)% actuarial 8 year local recurrence rate in the BCT N+ patients, who were not treated with adjuvant chemotherapy (Fig. 6). Such a reduction of local recurrence rate was also seen in the N+ cases treated with adjuvant chemotherapy in the RM-group (Fig. 7).

In Fig. 8, curves are given showing the effect of microscopic radicality of the excision specimen (microscopically tumour-free margins or tumour-positive margins) in the BCT patients. In the patients with microscopic irradicality the 8 year actuarial local relapse rate was 20(4)% versus only 9(2)% for those patients with microscopically tumour free margins.

No statistically significant effect of age on local recurrence rate could be found in both studied groups. In this study survival after salvage treatment in the locally recurrent cases was identical for both study arms (Fig. 9). A detailed report on quality of life will be published. In the evaluation over the years by the doctor a good or excellent cosmetic result was achieved after BCT in 81% (first evaluation one year after completion of BCT). This percentage dropped to 67% in the last recorded evaluation. Patient rating of the cosmetic result was better, (90%) good/excellent result in the first evaluation dropping to 80% in the last evaluation.

## DISCUSSION

This trial suggests that BCT with this specific combined treatment can be considered an acceptable option for stage II patients although the local recurrence rate is slightly influenced unfavourably by tumour size in the BCT group and not in the RM group. Together with data from the NSABP and from the Danish breast cancer group the results of this EORTC trial corroborated the conclusions on the validity of breast conservation for patients with larger tumours, which were formulated at the NCI Consensus Meeting of June 1990 [9].

Studying prognostic factors for local recurrence it was found in this study that size (T status) as a risk factor was of borderline significance in the BCT group, but not in those treated by mastectomy. Such a difference for the two arms was also seen for the nodal status as a predictor for local recurrence with the difference being more significant in the BCT group. The elevated risk for local recurrence in the N+ group of the breast conservation arm appears to be partly neutralised in the group receiving adjuvant therapy. As might be expected, completeness of excision (in the BCT group) is also a prognostic factor for breast recurrence, and this is certainly related to tumour size. Contrary to what is mentioned in the literature we did not find in our

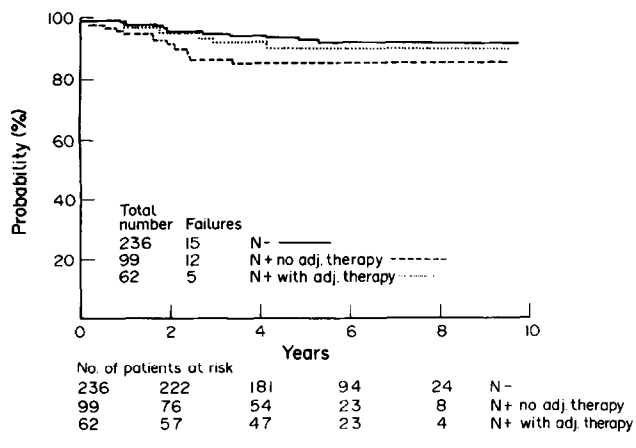


**Fig. 7. Time to local recurrence in the radical mastectomy cases split up in node negative patients and node positive cases with or without adjuvant chemotherapy. Logrank $P = 0.008$ (overall).**

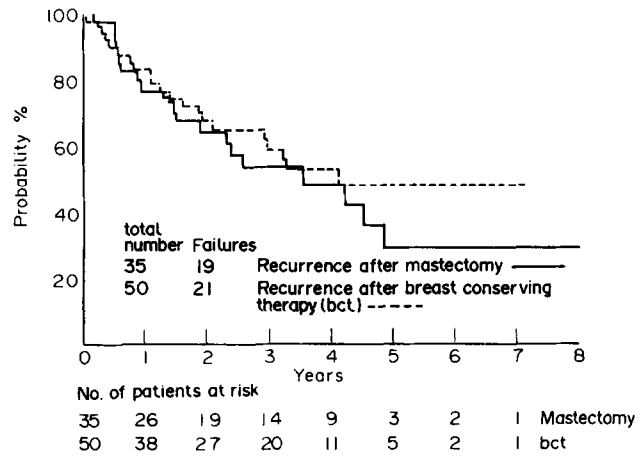


**Fig. 9. Duration of survival after salvage treatment for local recurrence in patients treated with breast-conserving therapy and with mastectomy in stage I and II breast cancer. Logrank $P = 0.49$.**

study any substantial effect of age on local relapse rate in either group. The above-mentioned differences in local recurrence risk between the two study arms might be less important when looking at local recurrences which are the first or only sign of treatment failure (see Table 3). It should be appreciated that the total number of local relapses is small and indeed included some appearing together with or after distant disease manifestation. The possible impact of size and nodal status on treatment choice therefore is restricted.

The importance of the mentioned prognostic factors will be studied in a multivariate analysis, which will be performed after completion of the pathology review. Extensive intraductal component (EIC) and other pathology criteria will then also be studied. In a recent interim evaluation the impact of EIC does not appear to be large in this study probably because of the high boost dose and the large boost volume.

The result of salvage treatment after local recurrence in this study does not appear to be better in the BCT group if compared with the results after salvage therapy for local recurrence in the RM group. However, it is too early to draw definite conclusions because of the relatively small numbers of local recurrences. This disappointing finding, which differs from literature data, suggests that there is a fair chance that many of the tumours in the patients with recurrent disease are in both groups of the same type and biological behaviour, locally relapsing irrespective of the treatment given.

The poor result of the treatment of recurrences in the BCT group might also be explained in part by the postulate that in these patients early diagnosis of local recurrence is hampered by fibrosis in the boost region as was frequently seen in our BCT cases.

Patients' satisfaction with treatment was high in the BCT group. Proper evaluation of quality of life will be addressed in a separate study.


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# Intermittent High-dose Tamoxifen as a Potential Modifier of Multidrug Resistance

**Michael J. Millward, Brian M.J. Cantwell, Ernst A. Lien, James Carmichael and Adrian L. Harris**

***In vitro* tamoxifen reverses multidrug resistance (MDR). To evaluate the clinical potential of using tamoxifen in this way, intermittent high-dose tamoxifen was combined with oral etoposide in 86 patients. At 320 mg/day tamoxifen for 6 days, mean plasma levels of tamoxifen in 11 patients increased from 453 ng/ml (range 269–664) on day 2 to 984 ng/ml (578–1336) on day 6. Of 31 patients who had plasma tamoxifen measured during the time of etoposide administration (days 4–6), 13 (43%) were over 1111 ng/ml (3 μmol/l), an active *in vitro* level. Potentially active levels of the principal metabolite, *N*-desmethyl tamoxifen, were also obtained but accumulation was slower. Emesis and thromboembolism were toxicities. Tamoxifen is a modifier of MDR, a role that warrants further clinical studies.**
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## INTRODUCTION

THE RESISTANCE of malignant cells to anticancer agents is a major cause of treatment failure in cancer. The multidrug resistant phenotype (MDR) is a form of cellular resistance characterised by reduced intracellular drug accumulation related to a cell membrane glycoprotein termed the P-glycoprotein which may be induced following exposure to a variety of structurally and functionally dissimilar cytotoxics such as etoposide, vinca alkaloids and anthracyclines [1, 2] with resulting cross resistance. Expression of the MDR has been shown to be correlated with clinical drug resistance in pretreated lymphoma, myeloma, leukaemia and soft tissue sarcoma [3, 4] and has been reported prior to any cytotoxic exposure in several tumour types including sarcoma, renal carcinoma, carcinoid tumours and breast cancer [4–6]. Thus strategies to overcome the MDR have the potential to benefit both