THE TRIAL

EORTC trial 10853 was started in 1986, and a total of 190 patients have so far been entered. To be eligible for the study patients had a biopsy which showed the presence of DCIS without invasion. Those with a lump or an area of microcalcification had the lesion completely excised. The lump or microcalcification had to be no greater than 3 cm in diameter. In all cases pathological examination of the original specimen, or a subsequent wide excision confirmed that the margins of the biopsy were free of DCIS. Surgeons were permitted to carry out axillary clearance or sampling if this was deemed necessary.

Patients were excluded if they had concurrent bilateral DCIS, or if the original presenting feature was Paget's disease of the nipple. Pregnant women were not entered into the study nor were those who had prior or concomitant malignancy, with the exception of basal cell carcinoma of the skin or cone biopsied carcinoma *in situ* of the cervix.

Only those ages less than 70 years were included, and those with mental conditions or social circumstances precluding long-term follow up were not asked to take part. All patients had pre-entry investigations including bilateral mammography, chest radiographs, full blood count and biochemical screen.

Patients fulfilling these criteria and who agreed to take part were randomised to receive no further treatment or to be given external beam radiotherapy to the affected breast not later than 12 weeks after wide excision. The radiation dose was 50 Gy given in 25 fractions to the entire breast. The axilla was not treated nor was a boost given to the excision site.

INELIGIBLE CASES

Details were sought from six of the main collaborating hospitals to find out reasons for exclusion of patients who at the time of the first biopsy were shown to have DCIS, without evidence of invasion.

These were 1. Centre Henri Becquerel, Rouen, France; 2. Antoni van Leeuwenhoekhuis, Amsterdam, The Netherlands; 3. Daniel den Hoed Hospital, Rotterdam, The Netherlands; 4. Longmore Hospital, Edinburgh, UK; 5. Guy's Hospital, London, UK; and 6. Centre Jules Bordet, Brussels, Belgium. These centres had entered into the study 30, 14, 13, 7, 7 and 6 patients, respectively.

The reasons for non-entry and distribution of cases from each of the collaborating hospitals are shown in Table 1. The commonest reason for ineligibility was incomplete excision, that is, the DCIS extending to the edge of the specimen. This was responsible for 48 patients (35%) not being entered into the trial. A prior breast carcinoma had been diagnosed in 25 (18%). Microcalcification was measured as extending mammographically for more than 3 cm in 16 patients (12%).

Because of the demands made on the histopathology departments to mark specimens and carry out multiple sections to determine completeness of excision and to exclude invasion, together with the differences in interpretation of different histological changes, there were 9 cases (6%) where the final report was not available before the deadline and so the patient could not be randomised.

Only 6 patients (4%) refused to take part in the trial after their informed consent was sought. A further 6 cases had palpable lesions which were greater than 3 cm in diameter. 4 patients were not entered because of protocol violation, and 5 had borderline lesions and were therefore not asked to participate. 4 patients were not entered because of protocol violation, and 5 had borderline lesions and were therefore not asked to participate. 4 patients were excluded because they were suspected to have infiltrating carcinoma, with positive fine needle aspiration cytology and mammography. Thus their treatment was planned for invasive disease. This is a problem which will sometimes occur when cytology is used to make a pre-treatment diagnosis. Prior non-breast malignancies had been diagnosed in 3 cases, and 2 patients had synchronous contralateral DCIS. 2 patients were unfit for further surgery and two were aged over 70 years.

Table 1. Reasons for non-entry

	AVL	CHB	DDH	GH	LHE	IJB	Total
Incomplete excision	13	14	—	5	16	—	48
Prior breast cancer	11	3	7	1	—	3	25
Microcalcification > 3 cm	4	4	1	1	5	1	16
Delay in histology	1	2	2	—	4	—	9
Multifocal DCIS	—	—	2	—	1	—	3
Patient refusal	1	1	—	—	4	—	6
Lump > 3 cm	5	—	—	1	—	—	6
Borderline lesion	—	4	—	1	—	—	5
Protocol violation	—	4	—	—	—	—	4
Suspected invasive cancer	1	—	3	—	—	—	4
Prior other malignancy	—	2	1	—	—	—	3
Contralateral DCIS	—	2	—	—	—	—	2
Unfit	—	—	—	—	2	—	2
Over 70 years	—	—	—	1	—	1	2
Doctor's omission	1	1	—	—	—	—	2
Uncertain biopsy margins	2	—	—	—	—	—	2
Total	39	37	16	10	32	5	139

AVL = Antoni van Leeuwenhoekhuis, CHB = Centre Henri Becquerel, DDH = Daniel den Hoed, GH = Guy's Hospital, LHE = Longmore Hospital, IJB = Institut Jules Bordet.

Table 2 summarises those cases who were not eligible for the trial because of the extent of DCIS. This comprised a total of 76 women so that 55% were ineligible because DCIS was too extensive. These patients were treated by total mastectomy which is still regarded by most surgeons as being the correct treatment for extensive or multifocal DCIS.

IMPLICATIONS

These data show that the stringent selection criteria of the trial have resulted in the exclusion of the majority of patients with DCIS presenting to breast clinics, all of which, except Longmore Hospital, were not associated with screening units. Thus the results of this study cannot necessarily be extrapolated to screen detected cases of DCIS. Nevertheless it does appear that symptomatic cases who prove to have DCIS have only a 50% chance that the disease can be widely excised and therefore be eligible for studies of breast conservation, of which there are several in Europe, and one in the USA (NSABP B.17) [5].

Table 2. Cases ineligible for trial because of extensive DCIS

Reason	No.
Incomplete excision	48
Microcalcification > 3 cm	16
Multifocal DCIS	3
Lump > 3 cm	6
	76

Does this mean that approximately half the patients with DCIS will need treatment by total mastectomy? This would seem to be illogical since it has been proven that patients with invasive cancers up to 4 cm in diameter can be safely treated by breast conservation. Why is it that patients with a condition in which they have a 30% chance of developing an infiltrating cancer are being offered ablative treatment, albeit with immediate or delayed reconstruction? The reason is that there is no body of data which has demonstrated that extensive DCIS can be satisfactorily treated, that is prevented from progressing to invasion by external or interstitial radiotherapy.

It could be claimed that the reverse is true, namely that patients with infiltrating cancer with associated extensive intraductal component are at greater risk of relapse after breast conservation including radiotherapy. However this may represent a different state from DCIS alone or with the earliest signs of micrometastases. No randomised studies are examining the role of either irradiation or tamoxifen for patients with extensive DCIS for which total mastectomy is the standard treatment at present.

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Tamoxifen Binding Sites Heterogeneity in Breast Cancer: a Comparative Study with Steroid Hormone Receptors

Giuseppe Leo, Gabriella Cappiello, Palmiro Poltronieri, Carmela Giardina, Corrado Manca, Carlo Storelli and Santo Marsigliante

Steroid receptors and tamoxifen binding sites (TBS) were assayed in the soluble fraction of 121 primary breast cancers. Scatchard analysis of TBS in high speed supernatant (100 000 *g*) showed one population of binding sites; however, biphasic plots were obtained in low speed supernatants (40 000 *g*). Isoelectric focussing of supernatants preincubated with radioactive tamoxifen identified two classes of TBS (pI 4.1–4.6) which have different binding affinities and bind neither oestradiol nor diethylstilbestrol. Association between TBS and steroid receptors was: TBS positive/progesterone receptor positive 32.6%, TBS positive/glucocorticoid receptor positive 52.7%, TBS positive/oestrogen receptor positive 60% and TBS positive/androgen receptor positive 72.2%. We conclude that heterogeneous TBS are present in low speed fractions and can be easily separated from the oestrogen receptor by isoelectric focussing. The association between TBS and steroid receptor status could be of clinical value in the management of primary breast cancer.
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INTRODUCTION

ALTHOUGH THE antitumoral effect of tamoxifen has been established in the management of advanced and early breast cancer [1], the exact modes of action of antioestrogen on breast cancer cells have not been completely elucidated.

Even though tamoxifen is thought to mediate its effects especially through the oestrogen receptors (ER), several aspects of tamoxifen action such as the response observed in 10% of patients whose tumours do not contain ER [2] suggest that non-oestrogen receptor mediated responses must occur in some tissues.

An alternative signal transmitter that is present in some ER negative tissues is the tamoxifen binding substance (TBS), first described by Sutherland and his colleagues [3]. Though the work of Sudo *et al.* [4] and Sheen *et al.* [5] strongly suggests that binding to the TBS is not an essential feature of the mechanism of action of antioestrogen, recently it has been reported that this binding site may represent a novel histamine receptor [6]. From this viewpoint, in addition to its effects mediated through binding to ER, tamoxifen may also exert antiproliferative effects through blockade of histamine responses.

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