Trials of Treatment for Non-invasive Breast Cancer

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Background

Twenty years ago, ductal carcinoma in situ (DCIS) and lobular carcinoma in situ (LCIS) were rarely diagnosed conditions, poorly understood and usually treated by mastectomy like all other breast cancers. During the intervening years important changes have occurred with regard to both invasive and non-invasive breast cancer. In particular, several trials have demonstrated the safety of breast conservation therapy for selected patients with unifocal invasive breast cancers measuring up to 4 cm diameter (Veronesi et al. 1995; Fisher et al. 1989; Van Dongen et al. 1992; Jacobson et al. 1995; Blichert-Toft et al. 1988). The paradox then became apparent that women with invasive cancers were being treated by breast conservation therapy yet those with the non-life-threatening DCIS were still being subjected to mastectomy.

Additionally, the value of mammographic screening was demonstrated in women aged 50 years or over (Nystrom et al. 1993; De Koning et al. 1995). Because of the presence of X-ray microcalcifications, 15%-20% of cancers diagnosed are DCIS (Anderson et al. 1991). The incidence of LCIS is almost unchanged since there are no radiodiagnostic signs of LCIS on mammograms. With increasing specialisation in histopathology, however, subtle changes at the borderline of atypical lobular hyperplasia and LCIS are being recognised so that a few more cases are diagnosed. It is now more generally understood that LCIS or lobular neoplasia is a marker of risk rather than an obligate precursor of invasive cancer (Page et al. 1991). For this reason, LCIS has been selected as one of the entry criteria in the International Breast Intervention Study (Fentiman 1989). In this trial, women at a two- to four-fold increased risk of breast cancer are randomised to receive either tamoxifen 20 mg or placebo for 5 years. The end-point is the number of breast cancer cases in the two arms of the trial.
Considerations in Designing the Trials

Against this background the EORTC Breast Cancer Co-operative Group set about designing a trial of treatment for DCIS in the early 1980s (Fentiman 1997). It was recognised that wide excision of DCIS would be a pre-requisite because limited excision had been shown to be associated with a 25% risk of development of invasive cancer (Betsill et al. 1978; Rosen et al. 1980; Page et al. 1982). Additionally, unless a wide excision was performed there was a danger that DCIS found in a biopsy was a near miss representing the non-invasive element of an invasive carcinoma. This might explain the high proportion of invasive cancers diagnosed early on in a series of DCIS treated by local excision and radiotherapy (Morgan et al. 1984).

In order to standardise histopathological handling of specimens a protocol of marking and sampling was drawn up by Dr. J. A. Peterse. The aim was to ensure that the specimen margins were systematically checked to minimise the risk of involved margins being missed.

All successful trials of breast conservation therapy had included axillary clearance so this procedure had to be considered as part of the surgical treatment. It was quickly dismissed. DCIS is by definition contained within the basement membrane of the ducts and has not attained the capability to break out of the normal domain of mammary epithelium. Hence neither vascular invasion nor axillary nodal involvement are accompaniments of pure DCIS. Although rare cases of axillary nodal involvement have been reported when the tumour was apparently pure DCIS, it is likely that foci of micro-invasion were missed, usually in more extensive lesions (Lagios et al. 1982). Since DCIS is not associated with axillary nodal involvement, not only could axillary surgery be omitted but so too could axillary irradiation. This would have an important consequence of reducing the morbidity of treatment within the trial.

With regard to the treatment of the breast itself, the randomised trials of treatment for invasive breast cancer had shown that a radiation dose of 46–50 Gy was adequate (Veronesi et al. 1995; Fisher et al. 1989; van Dongen et al. 1992; Jacobson et al. 1995; Blichert-Toft et al. 1988). With no available data on the radiosensitivity of DCIS, the dose was chosen arbitrarily as 50 Gy. Because the impact of radiotherapy on DCIS was unknown, the logical trial design was to compare breast irradiation with no radiotherapy in women who had had complete local excision of DCIS without evidence of micro-invasion. The basic trial design was thus:

Breast irradiation (50 Gy)

Complete local excision – Randomise

Observation

Unbeknown to the EORTC Breast Cancer Co-operative Group, at almost the same time the NSABP had started recruitment to B-17, a trial with similar inclusion criteria and treatment arms. Since then, various national groups