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For Debate

Radiotherapy for ductal carcinoma in situ detected by screening

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The national screening programme for breast cancer has led to women with asymptomatic ductal carcinoma in situ being detected and referred for treatment. This condition has an apparently excellent prognosis, but no precedent regarding treatment exists. A study in the United Kingdom has commenced comparing four treatments in patients with asymptomatic ductal carcinoma in situ (protocol available from the Cancer Research Campaign Clinical Trials Centre, Rayon Institute, London SE5 9NU). The four treatments comprise complete local excision alone, complete local excision plus tamoxifen, complete local excision plus radiotherapy, and complete local excision plus tamoxifen and radiotherapy. The trial will be a prospective randomised study incorporating a 2×2 factorial design, which permits evaluation of each additional treatment (figure). Participating doctors who think that either radiotherapy or tamoxifen is an essential or unacceptable treatment will be able to enter women in single randomisations for only one half of the trial. Can the use of radiotherapy be justified in this study when the course of the disease is poorly understood, the survival of patients is not in question, and serious doubts about the later effects of radiation exist?

In 1932 Broders defined carcinoma in situ as "a condition in which malignant epithelial cells and their progeny are found in or near positions occupied by their ancestors before the ancestors underwent malignant transformations."[1] Under a light microscope ductal carcinoma in situ appears as a carcinoma of mammary ducts in which there is no evidence of invasion through the basement membrane into the surrounding stroma.[2] An important problem, however, is that failure to show invasion into the stroma by microscopy does not mean that none is present, and careful histological examination of several sections is necessary before the condition can be diagnosed.

In the past patients with ductal carcinoma in situ presented with a mass in the breast and were managed by mastectomy. This approach was supported by the 60% incidence of residual ductal carcinoma in situ,[3] the 6-18% incidence of invasive carcinoma found in mastectomy specimens,[3,4] and the virtually 100% rate of cure after such surgery.[5] Even so, some patients have been managed less aggressively, and in a group of 25 women managed only by biopsy 28% developed invasive cancer within three to 10 years after biopsy.[6] When recurrence or invasive cancer develops, it tends to do so at or near the site of the original lesion, and provided that the patient is being carefully monitored such developments do not seem to prejudice survival. This point is of such importance as to have been the subject of a national survey by the American College of Surgeons, which found no statistical difference in five year rates of cure and survival when comparing 202 patients with ductal carcinoma in situ managed initially either by mastectomy or by less aggressive procedures.[7] Similar conclusions were drawn in a smaller British study of 28 cases.[8]

If the survival of women with ductal carcinoma in situ is not in doubt the justification for irradiation must be a reduction in the rate of local recurrence or in the development of invasive cancer. Some evidence exists suggesting that such reductions occur. In the national surgical adjuvant breast project 78 women with ductal carcinoma in situ were identified from the 2072 patients with invasive cancer enrolled.[9] Fifty one of the 78 women were managed by lumpectomy with or without irradiation, and seven of them developed recurrence at or close to the site of the initial lesions four to five months after surgery. Recurrences occurred in only two (7%) of the 29 patients who received radiotherapy but in five of the 22 patients managed by lumpectomy alone. Treatment failed in two women: one was managed by mastectomy and died from breast cancer at 62 months, and the other was managed by lumpectomy and irradiation and was alive with disease at 86 months after initial presentation.

Roentgen's discovery of *x* rays in 1895 led to their use in treating a wide range of malignant and benign conditions. Now radiotherapy is largely restricted to the palliation of symptoms in patients with advanced malignancy or to the cure of those with life threatening disease for whom other treatment either does not exist or is more toxic. Its use in benign disorders fell into disrepute because of potentially lethal late effects that may develop after treatment, in particular neoplasia induced by radiation. Regarding the breast, Read *et al* described the short term morbidity in 184 patients with small, primary breast tumours who were managed by lumpectomy and irradiation and commented on a 15% incidence of moderate skin erythema, a 56% incidence of mild to moderate breast discomfort, and a 9% incidence of pneumonitis. Of more serious concern are two reports that show a small but significant increase in mortality among patients with breast cancer managed by irradiation of the chest wall and mastectomy compared with those given only mastectomy,[11,12] a finding that became apparent only

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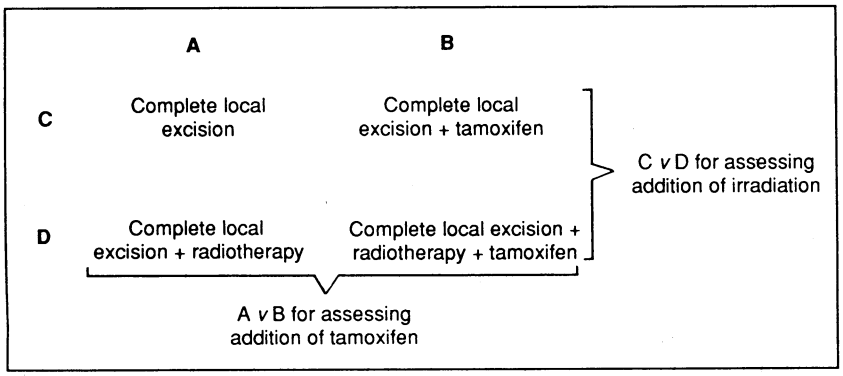

Design of United Kingdom randomised trial for management of ductal carcinoma in situ detected by breast screening

after 10 years of follow up. This excess death rate is probably due to an increased incidence of other tumours and an excess of deaths from cardiac failure due to the effects of radiation on the myocardium.

The study in the United Kingdom is selecting women with completely excised lesions for randomisation. To give healthy women who have volunteered for screening a five week course of radiotherapy, with its associated short term morbidity and its potentially more serious effects after treatment, seems hard to justify. Surely the scientifically and ethically sound approach in this uncommon disorder is a careful appraisal of the excised tissue after surgery and then close observation of the patient. In this way the course of the disease will be learnt, groups at high risk of progression identified, and public confidence in the screening programme maintained.

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Lesson of the Week

Fractures of long bones occurring in neonatal intensive therapy units

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To avoid fracturing long bones the utmost care must be used when handling premature infants during minimally invasive procedures

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Highly specialised intensive care and technology enable extremely premature and low birthweight infants to survive. The utmost delicacy must be used when handling these infants because the slightest trauma may cause fractures. We report on two premature infants who had fractures of long bones after insertion of an intravenous catheter.

Case reports

Case 1—A girl weighing 690 g was born at 25 weeks' gestation. She developed severe hyaline membrane disease requiring prolonged assisted ventilation, which was started when she was 6 hours old. Her other problems included septicaemia, a patent ductus arteriosus, and hydrocephalus resulting from an intraventricular haemorrhage. She required a combination of parenteral and nasojejunal feeding. Ten weeks after delivery an intravenous catheter was inserted into a peripheral vein in the dorsum of her left wrist. Swelling of soft tissue was noted subsequently, although the intravenous infusion was running normally. Radiography showed fractures of the distal metaphyses of the radius and ulna but no evidence of loss of bone density or thinning of the cortex (fig 1). The temporal relation between insertion of the catheter and the clinical and radiological evidence of the fractures indicated that they were traumatic in origin rather than a result of metabolic bone disease of prematurity. Before the fractures the serum alkaline phosphatase activity was normal and the serum phosphate concentration mildly raised at 1·69 mmol/l (normal range 0·8-1·4 mmol/l). The fractures were treated with immobilisation, and dietary supplements of calcium, phosphate, and vitamin D were continued. Satisfactory healing occurred without sequelae.

FIG 1—*Fractures of distal metaphyses of radius and ulna of left forearm, showing preservation of bone density and cortical margins*

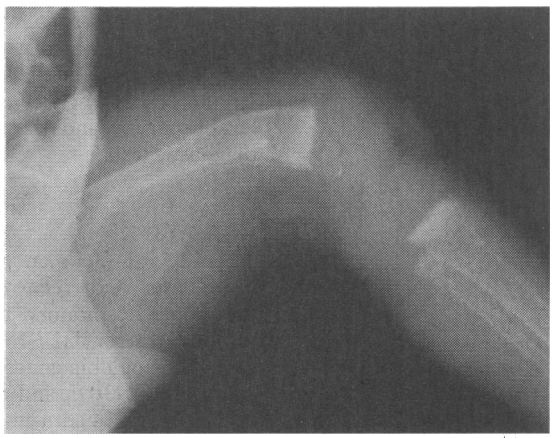

FIG 2—*Fractures of distal metaphysis and midshaft of left femur, with no radiological changes of metabolic bone disease of prematurity*

Case 2—A boy weighing 980 g was born at 29 weeks' gestation. He required assisted ventilation for hyaline membrane disease and persistent ductus arteriosus. He was fed through a nasojejunal tube and was given an intravenous infusion. On the fifth day after delivery the intravenous infusion was sited into a vein in the