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Accrual rate-limiting factors in a Swedish randomised ductal carcinoma *in situ* (DCIS) trial — a demographic study

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Abstract

In the last two decades the introduction of mammographic screening in the Western world has increased the number of diagnosed ductal carcinomas *in situ* (DCIS) considerably. *In situ* carcinoma of the breast is considered a heterogeneous disease, the natural history of which is not well known. Thus, appropriate treatment needs to be established. For this reason, a randomised trial studying the effect of breast conserving operation with or without postoperative radiotherapy was instituted in Southern Sweden in 1987. The aim of the present study was to assess patient accrual, identify limiting factors, and evaluate possible ways to influence these factors in order to increase patient accrual. Between 1987 and 1992, 331 patients had been registered with DCIS in the Regional Tumour Registry, 96 of which had been randomised. All 331 were subjected to chart review studying clinical data, mammography reports, cytology and pathology reports to identify inclusion and exclusion criteria according to the design of the trial. It was found that 5% (18/331) had an incorrect diagnosis of DCIS. According to the trial protocol 52% were not eligible (162/313). Fifty-eight per cent ($n=88$) of the 151 eligible patients had been correctly randomised. The most common reason for exclusion was lesion size. In 21% (66/313) the lesion was 'too large'. Several other limiting factors were identified such as in cytological and pathological definitions and reports, lack of information/awareness in certain physicians, patient reluctance to participate, which in turn may be influenced by the previous factor. With increased information to participating hospitals and considering the above given facts it should be possible to increase accrual from the 28% noted in the present consecutive demographic study to at least one-third of the diagnosed cases of DCIS.

Keywords: Breast cancer; Ductal carcinoma *in situ*; Intraductal carcinoma; Accrual; Randomised trial

1. Introduction

The natural history of breast carcinoma *in situ* is not well known. Until 15–20 years ago it was considered as a rare lesion constituting only a few per cent of diagnosed breast carcinomas. Like other carcinomas of the breast, these lesions were treated by mastectomy by most surgeons. With the introduction of mammography and mammographic screening the number of diagnosed *in situ* carcinomas of the ductal type (DCIS), has increased considerably. They now constitute some 15–25% of detected malignant breast lesions in mammography screened populations [1–3]. With the introduction of breast conserving therapy for small invasive breast carcinomas, it seems contradictory to treat *in situ* lesions, thought to be of lesser malignant potential, with mastectomy. Mastectomy as treatment for DCIS had been reported to result in 95–100% cure rates [4–6]. In contrast, retrospective benign biopsy studies indicated the development of invasive carcinoma in 20–60% of cases with up to 20 years' follow-up [7–9]. However, the patient numbers were small in these studies. Treatment protocols for patients with diagnosed DCIS showed loco-regional recurrence rates of 10–60% after excision only [10–22] and 5–20% after excision and radiotherapy (RT) [10,16,19,23,24] with follow-up times of 2–15 years. Approximately half of the recurrences were DCIS, half were invasive carcinomas. However, patient groups were selected and non-uniform. In studies where most patients had been diagnosed with clinical symptoms, recurrence rates seemed higher [10] than in those where asymptomatic women had been diagnosed with

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DCIS after a positive mammogram [11,12]. There are indications of biological heterogeneity within the DCIS group [25]. Hence, mastectomy seems to imply overtreatment for many women. Moreover, a proportion of the women with a small DCIS lesion (detected by screening) would probably never develop a clinical diagnosis of breast carcinoma in their lifetime. It is, therefore, imperative to conduct randomised clinical trials to study the effect of breast conserving therapy (BCT) with or without postoperative RT on the development of invasive carcinoma and mortality in this group of women. Because of previously limited knowledge of the age-related incidence of DCIS in the population, its histological patterns, extent, biological heterogeneity and the importance of a radical excision histologically, radiographically and clinically, accrual time for such a study was difficult to anticipate. A randomised DCIS trial was started in the Southern Health Care Region of Sweden on September 1, 1987, later integrated with the National Swedish DCIS Trial, launched in 1988. The aim of the present study was to: (1) assess patient accrual 4 years and 4 months after start of the trial; (2) identify limiting factors in patient accrual; and (3) to evaluate possible ways to diminish these factors.

To generalise results from randomised clinical trials is difficult if the trials only recruit a minority of the total cases that are eligible [26]. Unfortunately the proportion of included patients in relation to all that are eligible, as well as non-eligible, in a study area is rarely reported. One reason may be that the figure is not possible to assess because of a lack of tumour registries. In Sweden reporting of newly diagnosed cancer cases has been compulsory since 1958. A double reporting system is employed. The validity of registration of breast cancers in the Swedish Cancer Registry has been shown to be high [27,28], making it possible to analyse retrospectively all diagnosed cases of DCIS, randomised as well as non-randomised, to study selection bias.

2. Patients and methods

The Southern Health Care Region of Sweden has a population of 1.5 million, approximately one-sixth of the total Swedish population. There are eight local, five central and two regional hospitals treating all patients with breast carcinoma in the region. All hospitals are participating in the South Sweden Breast Cancer Group DCIS Trial named 'SBcis', which also implies a registration study of the non-randomised DCIS cases. Randomisation and registration are performed at the Regional Tumour Registry.

A mammographic screening trial has been in effect since October 1976 in the city of Malmö (population 230 000). When the present trial was started in September 1987, mammographic population screening for breast cancer was being considered for the whole region and was successively started, mainly for the age cohorts 50–74 years, during the time period studied. Since April 1990, population screening has been performed in the whole region with the exception of Malmö city, where screening of the trial control group started in August 1991.

2.1. Trial design and entrance criteria

Eligible in the study were patients with a diagnosed DCIS not exceeding one quadrant of the breast and operated upon with a breast conserving operation. Patients were randomised to either follow-up or to receive postoperative RT of 50 Gy. Previous or simultaneous ipsilateral or contralateral invasive or microinvasive breast cancer excluded the patient from the study. Other exclusion criteria were Paget's disease of the nipple, other malignant disease except for basal cell carcinoma of the skin and *in situ* carcinoma of the uterine cervix, pregnancy, psychosocial reasons or high age/somatic disease precluding RT or follow-up. Axillary clearance or biopsy was not requested. For lesions extending to one quadrant or more of the breast or if the lesion was smaller but appearing in a breast too small to permit an aesthetically acceptable breast conserving operation to be performed, simple mastectomy was recommended with or without immediate reconstruction. For DCIS patients not entered into the trial the recommended treatment was mastectomy or subcutaneous mastectomy (SCM) without axillary clearance.

2.2. Study population

During the study period 1 September 1987 to 31 December 1991, 331 patients with DCIS were registered at the Regional Tumour Registry (RTR). From mid-September to mid-December 1992 all 331 patients were subjected to chart review studying clinical data, mammography reports, cytology and pathology reports.

3. Results

During the study period 96 patients had been randomised. 8 patients had incorrect inclusion criteria or presented with exclusion criteria (Fig. 1). Thus, 88 patients were correctly included. Through chart review it was found that 18 patients did not have a correct diagnosis of DCIS (14 microinvasive ductal carcinomas, 1 invasive ductal carcinoma, 1 tubular carcinoma and 2 cases of lobular carcinoma *in situ*), thus leaving 313 cases of DCIS.

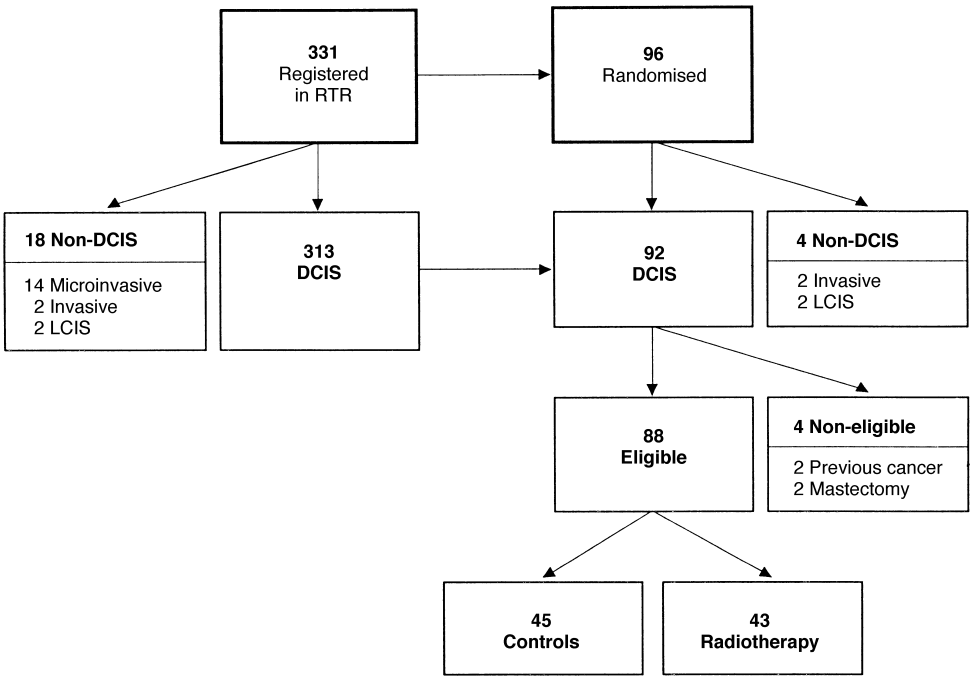

Fig. 1. Accrual into and protocol violators of the SBcis trial of Southern Sweden from the start on 1 September 1987 to 31 December 1991. DCIS, ductal carcinoma *in situ*.

Of the non-randomised 235 patients exclusion criteria were present in 172 (Table 1). In 66 patients the lesion was considered 'too large' for BCT, constituting 21% of the 313 correctly diagnosed DCIS cases during this time period.

39 patients had declared that they were not interested in participating in a randomised trial. 11 of these patients preferred mastectomy and 6 RT after BCT. 14 patients did not want RT (13 had BCT, one mastectomy as definitive treatment). In 8 cases treated with BCT the patient could not specify a reason for not wanting to participate. In 10 cases, the cytology report indicated carcinoma, which was interpreted as equal to 'invasive' and the patient was treated with mastectomy.

In 63 of the 235 non-randomised patients no exclusion criteria were present. From notes in the patients' charts there seemed to be hesitation on the part of the treating surgeon in implementing proper treatment based on the pathologist's report in 38 cases, although the patients were eligible for the study. In 8 cases, it was obvious that the treating surgeon was unaware of the present trial.

Table 2 depicts the number of randomised as well as non-randomised patients per year, the number increasing each year. The percentage of randomised patients compared with the total number diagnosed only varies between 25% and 35% with no obvious time trend despite the fact that the proportion of DCIS cases detected yearly by screening increased from 21% to 76% during the time period studied.

In the randomised group, 2 patients had had mastectomy before randomisation. The remaining patients had BCT. Twenty-one axillary dissections were performed (23%). Amongst the non-randomised DCIS patients 103 had BCT (47%), 33 of whom also had an axillary clearance. In 118 patients (53%), the breast had been removed together with an axillary clearance in 84 cases.

Table 1
Eligibility of patients diagnosed with ductal carcinoma *in situ* (DCIS) between 1 September 1987 and 31 December 1991 and not randomised into the SBcis trial of Southern Sweden

Total number of patients (n) = 331 Not randomised, (n) = 235 (71%)	n
Exclusion criteria present (n = 172) (52%)	
DCIS with microinvasion	14
DCIS combined with Paget's disease	11
Previous invasive breast cancer	9
Previous other malignant disease	11
Psychosocial impairment/high age/other somatic disease precluding RT	12
Lesion 'too large' for BCT	66
Patient did not want to participate in trial	39
Diagnostic cytology interpreted as invasive cancer — mastectomy was performed	10
No exclusion criteria present (n = 63) (19%)	
Hesitation/unawareness of trial	46
DCIS incorrectly randomised into invasive trials	4
Unknown reason for non randomisation	13

RT, radiotherapy; BCT, breast conserving therapy.

Table 2
Number of cases of ductal carcinoma *in situ* (DCIS) (randomised/non-randomised) diagnosed per year in Southern Sweden in relation to detection by screening

	1987[a]	1988	1989	1990	1991
Number randomised ($n=92$)	6	10	19	26	31
Detected by screening	3	2	16	23	26
Not detected by screening	3	8	3	3	5
Number not randomised ($n=221$)	18	26	53	66	58
Detected by screening	2	8	20	38	42
Not detected by screening	16	18	33	28	16
Total	24	36	72	92	89
Axillary clearance	9	13	34	40	42
% randomised/year	25%	28%	26%	28%	35%
% detected by screening/year	21%	28%	50%	66%	76%

[a] 4 months.

4. Discussion

From this analysis of 331 patients registered as DCIS at the Regional Tumour Registry of the Southern Health Care Region in Sweden during the time period of September 1987, when a randomised trial studying the effect of radiotherapy on DCIS after BCT was started, and the end of December 1991, it was found that 5% (18/331) of the patients had had an incorrect diagnosis of DCIS as judged from the pathology reports. According to the trial protocol, 162 of the remaining 313 DCIS cases (52%) were not eligible for the randomised trial. 88 patients had been correctly randomised out of 151 eligible (58%). With increased information and awareness of the study it should be possible to increase this figure further (Table 1). Amongst the cases considered 'too large' for BCT there seem to be several lesions that do not at all extend in one whole quadrant as judged from reading the pathology report. The pathologist has given vague descriptions of the size in more than half of the cases using words such as 'widespread' and 'diffusely scattered lesions', 'large extent' etc. instead of using figures in mm or cm to describe lesion size. This may reflect the actual difficulty in determining the size of such lesions that have often been expressed as 'multiple', 'multifocal', 'multicentric', etc. since definitions of these terms have varied [12,29,30].

With the intention to create a standardised protocol for handling of the specimens and to increase uniformity in the histopathological diagnosis, a review analysis of all slides with the pathologists involved was started in the Southern Health Care Region in 1991. Care has been taken to note crude characteristics of the lesions (nuclear grade, presence of comedo-type necrosis, architectural differentiation, extent in mm, distance to margin in mm, etc.) rather than categorising into subgroups to facilitate pooled analysis with other European and North American trials. The results of this review are in the process of being published. This standardised morphology protocol has been in prospective use since 1995. It is important that the pathology report is structured in such a way that all facts are reported and the most important points repeated in a summary comment, following the diagnosis, to decrease the risk of misinterpretation on behalf of the treating physician (Table 1).

With the present trial design, DCIS lesions of up to the size of one quadrant of the breast may be included. In large breasts this may make lesions of >5 cm eligible. It has not been fully established whether larger lesion size *per se* implies a worse prognosis, even if a few available treatment studies of small lesions show comparably low recurrence rates [11,12]. Lagios and colleagues [31] have shown that the likelihood of finding microinvasion in a DCIS lesion increases with size. Based on the experience of 333 patients with DCIS treated with BCT the van Nuys group has found significantly higher local recurrence rates for larger lesions [32]. The size distribution of lesions in both retrospective and prospective materials varies greatly. This may depend partly on varying methods of assessing size as well as the varying definitions of terms such as unifocal, multifocal, segmental, multicentric, diffuse, etc. It may also depend on whether a study accounts for DCIS lesions presenting with clinical symptoms or only screening-detected asymptomatic cases. These facts may have an impact upon the decision of the treating physician of whether or not to randomise a patient.

In previous years the main task of the cytologist was to decide whether the fine needle aspiration biopsy (FNAB) showed a malignant lesion or not. To differentiate between noninvasive and invasive breast carcinoma was of less interest before the introduction of BCT as treatment for breast carcinoma. However, in the present situation it is desirable, when possible, to use the information in the FNAB specimen to aid in the differential diagnosis of *in situ* as opposed to invasive breast carcinoma. Bondeson and Lindholm [33] have recently published a study of 300 breast cancer cases (199 invasive tumours, 101 DCIS). Using four cytological features a positive predicative value of 96% regarding invasiveness was seen when two or more of the features were present in a smear diagnostic of malignancy. This may be another way of increasing the number of 'eligible' patients in a study like the present one (Table 1).

The number of screening-detected cases increases sharply starting in 1989 (Table 2). In spite of this the proportion of randomised cases detected by screening does not seem to increase, the reason for this is not clear.

With increasing knowledge transferred to the treating physicians and other staff in the participating hospitals and being regularly repeated, it seems reasonable to

increase the accrual rate further in that increased knowledge should increase both patient and doctor compliance. In a recent study from Scotland [34] it was found that for almost 5000 patients with invasive breast cancer diagnosed between 1987 and 1993 12.3% had entered clinical trials. However, patients seen by surgeons with a high case load and those referred to an oncologist were approximately seven and three times, respectively, more likely to enter a clinical trial. Thus, specialist multidisciplinary team management should increase recruitment into clinical trials according to their conclusions. From our analysis, it may be assumed that with the present trial design for a randomised DCIS trial studying the effect of radiotherapy after BCT for DCIS lesions limited in size up to one quadrant of the breast, an accrual rate of at least one-third of the diagnosed DCIS cases could be expected. Fentiman and colleagues [35] published a study in 1991 on the eligibility of 216 DCIS patients from six European centres participating in the EORTC 10853 trial. They found that 64% were noneligible according to their entry criteria compared with 52% in our study. The most common reason was that the lesion was too extensive (73/216, 34%), which also was the case in our study (66/313, 21%). In their study 3% of the patients declined participation compared with 12% in our material. The participating centres of their study are all large cancer centres, whereas half of the hospitals in our region are local hospitals in smaller towns, many miles from the radiotherapy clinic. Of interest, recent analysis of the EORTC 10853 data by Bijker and colleagues [36] shows varying accrual rates from 7% to 66% between the four major participating institutions. They suggest these results are due to differing interpretation of selection criteria in the different centres. We have also noted a variation in the accrual rates. If we analyse the accrual rates from the five major contributing hospitals (38–78 cases of DCIS per hospital), there was a variation between 9 and 45% (median: 29%). Highest accrual rates were seen where mammography screening centres were well integrated with specialist breast clinics.

The results of the NSABP-B17 trial on the effect of RT after BCT for DCIS were published in 1993. A significantly higher frequency of recurrences was seen in the group not having received RT, results that have been confirmed in a later follow-up [37]. No detailed information was initially given on distance to margins, histological growth type, nuclear grade, etc. which may be of importance concerning reappearing ipsilateral DCIS or invasive carcinoma. These results might, however, have influenced the inclusion rate of our study thereafter. In November 1997, 200 cases had been randomised in SBcis. 96 had thus been included during the first 52 months and 104 during the following 70 months instead of an expected 129, had the inclusion rate been unchanged.

DCIS is still considered to be a radiologically, histologically and biologically heterogeneous disease with insufficient information to support any one treatment option as being superior [25]. The results from the NSABP-B17 study need to be confirmed in other studies. It is thus essential that ongoing prospective DCIS trials are optimally conducted and analysed to enable sound conclusions to be drawn concerning the appropriate treatment for the individual woman with DCIS. Continuous information to involved hospitals and physicians to assure proper accrual is an important prerequisite towards this goal.

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