

**Uncertainties in the management of
screen-detected ductal carcinoma in situ**

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PREFACE

This publication brings together experience of screen-detected ductal carcinoma in situ (DCIS) gained over the past 20 years of the NHS Breast Screening Programme (NHSBSP). It reflects current understanding and uncertainties about the management of women with screen-detected DCIS and describes the Sloane Project, which is a UK-wide prospective audit designed to address some of the uncertainties concerning the diagnosis and treatment of DCIS. It is intended that the publication will be a useful source of information about DCIS and that it will encourage participation in the research initiatives.

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Chapter 2 is based on the protocol for the BASO DCIS II study and is published with kind permission from Professor Nigel Bundred. The trial has now closed to further recruitment.

The NHSBSP is grateful to Karen Clements (Sloane Project manager) for her help in summarising the Sloane Project protocol for this publication. The full study protocol with appendices (Version 9 January 2008, authors Karen Clements and Olive Kearins) is on the Sloane Project web site (www.sloaneproject.co.uk).

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1. DIAGNOSTIC UNCERTAINTIES

1.1 Background

The introduction of mammographic screening has been associated with a large rise in the apparent incidence of ductal carcinoma in situ (DCIS). Approximately 20% of screen-detected cancers in the National Health Service Breast Screening Programme (NHSBSP) are in the form of DCIS.¹ The proportion of screen-detected cancers that are detected as DCIS is also associated with age; the younger the screening population, the higher the proportion of DCIS detected. Since the beginning of the NHSBSP there has been a great deal of debate concerning the value for the patient of detection of DCIS;^{2,3} some have argued that detection of this stage of breast carcinoma often represents overdiagnosis (detecting disease which would never become clinically apparent or threaten life) and causes anxiety and physical harm (unnecessary surgery). Others suggest that detection of DCIS is important because they believe that it is an obligate precursor of invasive carcinoma.

Importantly, there is also conflicting evidence regarding the optimum treatment for such impalpable in situ lesions, which remains despite several large clinical trials. Unresolved issues include the optimum margin of surrounding normal tissue which is required in order to classify the disease as completely excised,^{7,8} the need for radiotherapy for all patients who have had breast conserving therapy and the value of hormone therapy in subsequent management. In addition, the patient with DCIS may have to deal with clinical uncertainty and complicated medical/clinical concepts beyond those encountered by women whose lesion is clearly an invasive cancer.

These factors, and the technical difficulties of making a preoperative diagnosis and localisation of such lesions, have meant that DCIS remains a controversial and difficult topic. Effective treatment of patients with DCIS requires a high level of multidisciplinary team working between the radiographer, radiologist, surgeon and pathologist as well as breast care nurses and all staff involved in the care of such patients.

1.2 Preoperative diagnosis

For the radiologist, the main difficulties are obtaining a preoperative diagnosis and assessing lesion size. Low grade lesions, even when sampled correctly, may yield biopsy results of atypical ductal hyperplasia (ADH) owing to the small amount of abnormal tissue provided for the pathologist. This difficulty in obtaining a definitive histological diagnosis, even with more widespread use of core biopsy, has led to the introduction and use of vacuum assisted devices in many breast screening units. Such devices provide a greater amount of tissue, which is particularly important to the pathologist for the diagnosis of low grade intraductal epithelial proliferations and reduces the upgrade rate from ADH at percutaneous biopsy to DCIS at surgery by half.^{9,10} The use of vacuum assisted biopsy equipment reduces the rebiopsy rate substantially, which helps offset the increased costs associated with the use of such devices.

An additional practical difficulty is either predicting or preoperatively diagnosing the presence of an occult invasive focus within an area of

DCIS. Ultrasonography of areas of calcification may reveal a mammographically occult mass representing occult invasion, but this is not always the case. There is evidence that the use of vacuum assisted biopsy devices approximately halves the 'upgrade rate', ie cases diagnosed as DCIS at percutaneous biopsy but subsequently found to have invasive disease at therapeutic surgery.¹¹ The grade of DCIS at percutaneous biopsy and the extent and number of mammographic calcifications have been shown to be helpful in predicting which DCIS cases will contain occult areas of invasion.¹²

The identification or prediction of radiologically occult invasive foci clearly has important implications for the performance and timing of surgical axillary lymph node procedures. Axillary surgery may have to be undertaken as a second operation if invasive disease which had not been recognised or predicted preoperatively is found to be present in association with DCIS in the breast excision specimen. Conversely, axillary lymph node dissection is not appropriate for patients with pure DCIS. A number of centres are assessing the role of sentinel lymph node biopsy in patients with a pre-operative diagnosis of high grade DCIS.

The assessment of lesion size on mammography is known to be inaccurate, especially in the case of low grade DCIS, which often calcifies only partially if at all. Studies of the value of magnetic resonance imaging (MRI) in both DCIS detection and lesion size assessment have shown similar problems with the recognition and estimation of the dimension of low grade DCIS. Recent studies have also indicated that MRI can detect DCIS lesions that are not visible mammographically.¹³ However, despite advances in breast imaging, it remains the case that patients with DCIS more often than those with invasive carcinoma require second operations to obtain margins which are free of disease; the extent of the DCIS may be previously unsuspected as no calcifications have been seen in the more peripheral areas of the disease.

Preoperative lesion localisation of DCIS is also more difficult than invasive cancer; often these investigations have to be performed under stereotactic control and the absence of a defined mass means that wire migration is more likely to occur. The use of ultrasound visible markers deployed during stereotactic biopsy and radioisotope lesion localisation may aid preoperative localisation of DCIS lesions in the future.

1.3 Histopathological assessment

Histopathological assessment of atypical intraductal epithelial proliferations may be challenging. Making a preoperative histological diagnosis of DCIS on the basis of one or only a few abnormal duct spaces may be difficult, and is often more complex than establishing a diagnosis of invasive cancer. Although high grade DCIS can be diagnosed when only a single duct space contains highly abnormal and pleomorphic cells, particularly if associated with central comedo necrosis, a great deal of caution must be taken in making such a diagnosis on a limited tissue sample. The NHSBSP Pathology Reporting Guidelines for non-operative

diagnosis should be followed,¹⁴ and in the rare problematic cases which cannot be resolved with additional levels and immunochemistry, a preoperative diagnosis of suspicious (B4) rather than malignant (B5) should be provided. This is especially true of intermediate or low grade intraductal epithelial proliferations where the range of possible categories ranges from B3 to B5 and training and expertise are required.

Despite these difficulties, the reproducibility of a diagnosis of DCIS is substantial, as shown in the NHSBSP Histopathology EQA scheme.¹⁵ The particular areas of difficulties for the histopathologist lie in the assessment of DCIS lesion size and assessing distance of the lesion to the surgical margins of excision. The histopathologist is, like the radiologist, to some extent reliant on targeting the areas of microcalcification. Specimens excised for the management of DCIS are the most difficult breast specimens for the histopathology laboratory to handle and require time, resources and experience. It is not possible to handle every sample excised for microcalcification in the same manner, and each must be examined according to variable features such as the size and shape of sample, the radiological abnormality, the surgical procedure undertaken, the extent of the disease and the previous histological appearances/preoperative diagnosis, to name but a few. It is therefore not possible to be prescriptive regarding a single optimum method of pathology specimen handling. A range of different protocols are in use in histopathology laboratories, and experience and judgement are required to select the best methodology for any one sample. Because of this variation, however, central review of DCIS histopathology is often impossible with respect to factors such as size of lesion and margin status, as shown by the problems encountered during the central review of cases in the UKCCCR DCIS I trial. Thus, partly as a result of this necessary variation in handling individual samples from patients with DCIS, there is an innate difficulty in obtaining high quality data from retrospective clinical trials of DCIS.

In addition to the histopathological difficulties of specimen handling and assessment of lesion size and distance to margins, the NHSBSP Histopathology EQA scheme demonstrates that the reproducibility of assessment of high grade DCIS is moderate; however, the classification of intermediate and low grade disease is only fair, and this remains an area of concern for histopathologists.¹⁵

The role of hormone therapy in the management of patients with DCIS remains unclear; this has consequences for the pathology laboratory assessment of hormone receptors in the disease. Early analysis from the Sloane Project has shown that 71% of centres providing data to date are assessing hormone receptor(s) on some or all cases of DCIS. However, the immunohistochemical methodologies and, in particular, the scoring systems and cut-offs applied are not standardised.¹⁶ This has significant implications for the interpretation of clinical data in this area.

2. TREATMENT OPTIONS

2.1 Optimum treatment

The treatment of DCIS is fraught with difficulty and, unlike invasive breast cancer, there is much less agreement regarding optimum tailored therapy. It is generally agreed that adequate local treatment comprises either simple mastectomy alone or complete microscopic tumour excision and radiotherapy. Although radiotherapy has been shown to reduce the risk of recurrence, many clinicians are reluctant to use it in all patients due to the lack of evidence that it affects mortality. In the UK only 30% of patients with DCIS receive radiotherapy, whereas elsewhere in Europe and in the USA it is standard therapy¹⁷. Moreover, there is no agreed definition, either nationally or internationally, regarding an accepted margin of excision which one would wish to obtain, and this remains an area of significant controversy.^{7,8}

2.2 The role of surgery

In the UK, 30% of women diagnosed with screen-detected in situ cancer (non-invasive or microinvasive) are treated by mastectomy and 70% by breast conservation. This compares with 26% of women with screen-detected invasive cancer who are treated by mastectomy and 72% by breast conservation.¹⁷

Mastectomy is an excellent treatment for DCIS, but many would consider the loss of a breast for a woman without invasive cancer an overtreatment. Performing wide local excision on patients with DCIS is technically more challenging than in the case of patients with an invasive mass lesion. The surgeon is usually unable to feel the lesion, even after the skin is incised, and the difficulties of wire placement make accurate excision more difficult. As discussed previously, interpretation of specimen radiography during surgery is particularly difficult in DCIS cases. As incompletely excised DCIS may recur as invasive disease, the price of inadequate surgery may be extremely high.

2.3 The importance of surgical margins

In the four trials reported to date (all commenced in the 1980s) negative surgical margins were present in 63% NSABP B17 patients, 75% NSABP B24, 70% UKCCCR and 79% of those in the EORTC trial. In the pathological review of the NSABP B17 trial, involved margins were associated with a two-fold increased risk of recurrence even after radiotherapy.¹⁸ Margin involvement predicted recurrence in the first five years and when combined with nuclear grade and/or marked comedo necrosis identified risk of local recurrence.¹⁸ In the low risk group radiotherapy effected a 7% absolute reduction in overall recurrence at eight years (ie <1%/year).¹⁸ In the EORTC trial when patients had clear margins (> 1 mm), recurrence was 15.6% at eight years in the absence of radiotherapy and 10% in the presence of radiotherapy.¹⁹ The relevance of the aforementioned DCIS trials to clinical practice is limited and variability in specimen processing, pathological assessment, heterogeneity of surgical technique and eligibility criteria differ. The lack of data on actual tumour-free margin width is a major shortcoming. Silverstein has argued that clear margins (> 10 mm clearance), small size (<2 cm) and absence of comedo necrosis in a DCIS lesion are associated with a low risk of recurrence which is not significantly different from similar lesions treated with radiotherapy.^{20,21}

In the UKCCCR DCIS trial clear margins had an overall 14% recurrence rate compared with 23% when margins were involved, and the overall invasive recurrence rate at four years for low risk grade 1 and 2 DCIS was 4% (S Pinder, J Cuzick, personal communication). No prospective study of the margin width needed to minimise recurrence has been undertaken in invasive or in situ cancer. Retrospective studies in invasive cancer suggest that any margin of clearance greater than 1mm is sufficient in women over 50 years of age.^{19,22–25} Clear margins (>1 mm) are associated with a low 7% recurrence rate at five years compared with a 36% recurrence rate when margins are involved regardless of the use of adjuvant radiotherapy.²⁶ Thus the starting point for any new trial must be clear surgical margins if recurrence from ductal carcinoma in situ is to be minimised. Whilst accepting that the addition of radiotherapy applied to clear margins will lower recurrence rate, the overall benefit/risk for women with clear margins has not been studied. Does margin width matter? Notably in the last DCIS trial only 14% of women had clear margins >5 mm (S Pinder, personal communication), a finding similar to the EORTC trial.¹⁹ Moreover wide margins >1 cm will inevitably compromise cosmesis and patients' body image perception.²⁷ This will have economic consequences for the NHS since between 30% and 50% of DCIS patients currently undergo re-excision to achieve clear margins variously defined as between 1 and 10 mm clearance.²⁷ Any reduction in required excision margin width from 10 mm will reduce the re-excision rate and associated treatment costs.

2.4 The role of radiotherapy

DCIS has become an increasingly common diagnosis following the advent of mammographic screening.²⁸ Among symptomatic patients it constitutes some 3% of breast cancers, but in the United Kingdom DCIS currently accounts for 20% of screen-detected cancers, and similar figures have been found in the United States. It is generally agreed that adequate local treatment comprises either simple mastectomy alone or complete microscopic tumour excision and radiotherapy.²⁰ Although radiotherapy has been shown to reduce the risk of recurrence, many clinicians are reluctant to use it in all patients; indeed BASO audit figures¹⁷ show that only 30% of UK patients with DCIS receive radiotherapy. For localised DCIS most clinicians consider mastectomy to be overtreatment and the focus of current research is to determine and identify which DCIS lesions require additional treatment after complete local excision. However, the rate of recurrence after breast conserving surgery for DCIS in the absence of radiotherapy remains high (20% at 10 years).^{6,20,29} Three major trials (NSABP B17/EORTC⁴/UKCCCR DCIS⁵) have demonstrated the role of adjuvant radiotherapy in reducing local recurrence of DCIS and the development of ipsilateral invasive cancer in the group which received radiation. Radiotherapy guidelines for locally excised breast DCIS are based on the results of three major prospective randomised trials involving 2827 women conducted by the NSABP, EORTC and UKCCCR. Although there has been no meta-analysis, the trials offer consistent evidence for approximately 50% reduction in the rate of total (intraduct plus invasive) ipsilateral tumour recurrence. International practices for radiotherapy are at present based on the primary analysis and apply across all groups recommending 50 Gy in 25 fractions to the whole breast after complete microscopic excision of DCIS. None of the trials are prospectively

designed to identify high or low risk subgroups and the frequency of complete local excision ranged from 63% in NSABP B17, to 70% in the UKCCCR trial, and 79% in the EORTC trial. None of these trials have yet demonstrated the ability of radiotherapy to prevent distant metastases or death from breast cancer.^{19,30} By 12 years follow up deaths from breast cancer in the NSABP B17 Study (818 randomised) occurred equally in both arms and represented 27/88 (30%) total deaths. In fact deaths after treatment for DCIS in the USA are dropping.²⁸

2.5 Is radiotherapy necessary for all women?

Whereas failure to give radiotherapy after invasive breast cancer leads to a 40% local invasive cancer recurrence rate at 5–10 years and increases cancer mortality, recurrence after DCIS is not associated with increased cancer mortality.^{4,6} Fifty per cent of all local recurrences after DCIS wide excision is DCIS (with no threat to life) and in the other 50% invasive breast cancer, amounting to an overall invasive recurrence rate of 10% in high risk and 5% in low risk DCIS at five years. However, 95% of low and intermediate grade DCIS is ER positive and in the EORTC study, invasive relapses largely retained the initial DCIS ER status.¹⁹ Since screen-detected breast cancers in the UK have an overall 90% eight year survival¹⁷ and all women on DCIS follow up will have yearly mammography, it is unlikely that invasive recurrence will compromise survival. Thus the overall likelihood of increased breast cancer mortality by omitting radiotherapy in low risk DCIS is small but radiotherapy side effects will occur in at least 10% of patients since radiation morbidity can occur irrespective of a patient's disease prognosis. There is thus a trade-off between potential radiotherapy side effects to the whole population against adverse events of (treatable) local recurrence and its consequent psychosocial sequelae. Retrospective evidence from the randomised trials exists that selective clinicopathological features, of which excision margins are the most important (but also including patient age, comedo necrosis and nuclear grade), can be reliably combined to classify women by risk group. Women with annual hazards of relapse less than 2% are considered low risk and those greater than 2% high risk one year after complete microscopic excision alone.^{21,26} Additionally, older women > 50 years of age have a lower risk of recurrence.^{5,31} Indeed in an analysis of UK screen-detected DCIS women treated by breast conserving surgery in one centre, only excision margins and tumour grade were independent statistically significant predictors of recurrence.²⁶ Thus, there is a need to identify in low risk subgroups whether a policy of observation can be used as an alternative to whole breast radiotherapy after primary surgery. Additionally, the recent NSABP B24 pathological analysis of relationship of oestrogen receptor positivity to prevention of relapse by tamoxifen has identified a 60% reduction in relapse rate in women on tamoxifen who had ER positive DCIS but no effect of tamoxifen on oestrogen receptor negative DCIS.³² It is likely that adjuvant endocrine therapy will reduce relapse risk in oestrogen receptor positive patients to such low levels that a further relative 50% reduction in recurrence risk after radiotherapy will contribute little additional absolute benefit (eg annual ipsilateral invasive breast recurrence risk reduced from 1% to 0.5% by radiotherapy).

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The key issue is whether this small absolute reduction in the risk of recurrence justifies giving radiotherapy to all. Whilst a recurrence is distressing to the patient, local recurrence after treatment of DCIS is not life threatening – none of the trials have shown any difference in survival between the irradiated and non-irradiated arms despite the higher risk of recurrence in the latter group. In contrast, all irradiated patients are exposed to the potential morbidity of radiotherapy, such as breast oedema, breast shrinkage, tenderness, etc.^{33,34} The full effects of this have not been quantified since the original trials of radiotherapy following wide local excision for invasive disease did not include detailed quality of life focusing on symptomatology in the irradiated breast. Nor were cardiac effects recorded, although modern techniques exclude the heart from the treatment volume.³⁵ In the UK there has been a reluctance to use radiotherapy in view of the lack of evidence that it affects mortality whilst elsewhere in Europe and the USA it is standard therapy. It is important for current UK protocol that the appropriate tumour treatment for low risk DCIS patients is identified since the percentage of patients treated with radiotherapy is likely to increase in the light of the result of the UKCCCR DCIS trial.⁵

2.6 Quality of life and health economic consequences

The quality of survival may be affected by radiotherapy, and there is a balance of trade-offs between local relapse and radiotherapy effects, including local breast symptoms, body image concerns and general symptoms such as fatigue. Psychosocial studies of the effect of DCIS and its treatment are lacking^{36,37} and it is unclear whether or not the psychological impact of this condition is equivalent to that of invasive breast cancer.³⁷ On the one hand, women are told of a good prognosis but on the other they need treatments equivalent to invasive breast cancer. In a retrospective study of breast conserving/radiation treatment, subjective evaluation of cosmesis was generally good but those patients with body image concerns had worse sexual functioning.³⁸ Accurate knowledge of the quality of life (QL) of these patients treated with or without radiotherapy would contribute to the identification of best treatment and aid informed decision making.

The clinical balance associated with the routine use of radiotherapy in women with completely excised ER positive DCIS is also reflected in terms of cost-effectiveness: the additional cost of and morbidity associated with radiotherapy needs to be balanced against the cost and negative health effects of potentially increased recurrence from not using radiotherapy. It is anticipated that withholding radiotherapy from this group of women is likely to be extremely cost-effective, as the estimated costs of treating 100 such patients with radiotherapy (including simulation) is approximately £200,000, compared with the £12,000–£20,000 that would be required for 3–5 mastectomies following recurrence (assuming a 3–5% increased recurrence rate from omitting radiotherapy). There are also costs of treating side effects of radiotherapy, which are estimated to occur in at least 10% of women.

2.7 The significance of oestrogen receptor status

Pathological review of oestrogen receptor status in a subset of the NSABP B24 patients reported that 75% of DCIS is ER positive.³² There is a strong correlation between grade of DCIS and oestrogen receptor expression, with the vast majority (90%) of low and intermediate grade DCIS lesions being ER positive whereas 50% of grade III DCIS is ER negative.³⁹⁻⁴¹ Comedo necrosis within DCIS is associated with an increased recurrence rate and is more often associated with ER negative grade III DCIS.^{39,41} However, Van Nuys grading did not improve on nuclear grade in the prediction of recurrence in the UKCCCR DCIS trial.⁵ In invasive disease hormonal therapy benefits only those which are ER positive and laboratory studies have demonstrated that anti-oestrogens significantly reduce proliferation of ER positive DCIS but have no effect on ER negative lesions.⁴² In addition, studies of hormone replacement therapy withdrawal at diagnosis prior to surgery have shown a decrease in proliferation in ER positive DCIS, but not ER negative DCIS on excision.⁴⁰ In the UKCCCR DCIS trial, in which oestrogen receptor status was not measured, tamoxifen reduced the incidence of recurrent DCIS (RR 0.68, 95% CI 0.49–0.96) but not invasive cancer.⁵ A pathological review of oestrogen receptor status in the NSABP B24 trial identified that while tamoxifen reduced the risk of recurrence in ER positive DCIS by 60% (RR 0.41, 95% CI 0.25–0.68), it had no apparent effect on relapse rate in ER negative DCIS.³² Thus, in ER positive patients systemic anti-hormonal therapy (anti-oestrogen or aromatase inhibitors) may be sufficient to prevent the majority of local relapses in ER positive DCIS and reduce further the benefit of radiotherapy. Patients with DCIS essentially have a good prognosis and the majority (90%) will not develop invasive disease at 10 years.^{35,40} However, they have an excess risk of contralateral breast cancer.³⁷ The contralateral breast cancer rate in the NSABP B17 and NSABP B24 studies of DCIS remains significantly greater than that in the NSABP P-1 trial.^{18,31,43} However, in the 2003 overview/meta-analysis,⁴⁴ tamoxifen only prevented contralateral breast cancer in women with ER positive tumours.

2.8 The benefits of adjuvant endocrine therapy

In the UKCCCR DCIS trial low and intermediate grade lesions given tamoxifen alone had a similar risk of recurrence to those given radiotherapy alone. This may reflect that 90% of low and intermediate DCIS is likely to be ER positive and hence benefited from adjuvant tamoxifen. In women undergoing tamoxifen therapy for DCIS after breast conserving surgery and radiotherapy (NSABP B24 trial) a significant reduction in absolute relative risk of recurrence was seen overall but this was largely due to a 40% reduction in recurrence in women under 50 years of age on tamoxifen, whereas a non-significant 20% reduction was seen in women over the age of 50 randomised to tamoxifen.³¹ This contrasts with a 50% reduction in recurrence rate in this study if the margins were clear. In the UKCCCR DCIS trial 90% of the patients were aged over 50 and a non-significant 20% reduction in risk of recurrence in patients randomised to tamoxifen was seen (a similar figure to that seen in the NSABP B24 trial). The results from randomised trials in which oestrogen receptor was not prospectively determined contrasts strongly with

retrospective review of the NSABP B24 trial in which a 60% reduction in overall recurrence rate was found in ER positive (but not ER negative) DCIS treated by tamoxifen. There is an urgent need to determine the benefit of radiotherapy in low risk ER positive DCIS patients who are undergoing adjuvant endocrine therapy. The presence of the type 1 tyrosine kinase receptor oncogene HER2 has been associated with an increased resistance to tamoxifen⁴⁵ (the drug used in the DCIS trials). Since 70% of DCIS lesions express HER2³⁹ it is possible that there could be increased resistance to tamoxifen in this subgroup even in the presence of the oestrogen receptor.⁴⁶ Newer compounds such as aromatase inhibitors act systemically to inhibit oestrogen synthesis in the tissues. These compounds prevent oestrogen biosynthesis by inhibiting the enzyme aromatase, which catalyses the conversion of androgen androgens (androstenedione and testosterone) to oestrogens (oestrone and oestradiol).^{47,48} The removal of oestrogen from cancer cell lines which are ER positive and overexpress HER2 has been shown to be effective in inhibiting proliferation whereas the addition of tamoxifen has had the reverse effect.⁴⁶ In a phase III trial comparing the aromatase inhibitor letrozole and tamoxifen in patients with ER positive invasive tumours, women who were HER2/1 positive responded well to aromatase inhibition but infrequently to tamoxifen.⁴⁹ This suggests that HER1 and HER2 affect signalling through the oestrogen receptor and that the growth-promoting effects of these receptor tyrosine kinases on ER positive breast cancer can be inhibited by aromatase inhibitors but not always by tamoxifen. In theory, therefore, aromatase inhibitors should be a better strategy in DCIS lesions, which are not only ER positive but in 60–70% of cases express ErbB2. Additionally withdrawal of hormone replacement therapy (HRT) in ER positive DCIS has been shown to cause a fall in epithelial proliferation.⁴⁰ Newer third generation aromatase inhibitors have good efficacy in advanced breast cancer and are in general better than tamoxifen in this setting.^{47,48} They offer another approach to local control, prevention of recurrence and the prevention of primary breast cancers, which may be superior and/or complementary to the use of tamoxifen. Anastrozole is a potent new non-steroidal aromatase inhibitor, which is highly selective, well tolerated, and effective in treating advanced breast cancer.^{47,48} In postmenopausal women, a daily dose of 1 mg anastrozole produces oestradiol suppression of greater than 80% using a highly sensitive assay.^{47,48} Anastrozole does not possess progestogenic, androgenic or oestrogenic activity and in the adjuvant ATAC trial anastrozole significantly reduced contralateral breast cancer compared to tamoxifen.

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3. SLOANE PROJECT

3.1 Project rationale

The Sloane Project is a UK-wide national audit of the diagnosis, radiological and histopathological reporting and clinical management of DCIS. Data collection of the rarer histopathological disease entities that in the past were regarded as reflecting an increased risk of developing invasive breast carcinoma bilaterally, such as lobular in situ neoplasia (atypical lobular hyperplasia and lobular carcinoma in situ) and atypical ductal hyperplasia, are also included. The presentation, diagnosis and behaviour of these entities are also imperfectly understood, and the national collection of reliable and accurate information on these will maximise this data resource.

The Sloane Project is an innovative, prospective data collection from women with in situ breast carcinoma and high risk atypical epithelial proliferations detected through the NHSBSP. It was devised by Mr Hugh Bishop, who heads the multidisciplinary steering group, as a result of recognition of the need for high quality data from all aspects of the diagnosis and management of patients with DCIS. The project is named after the late Professor John Sloane, an internationally recognised breast histopathologist with an interest in DCIS. The project is administered through the West Midlands Cancer Intelligence Unit.

It is intended that this national audit will form a unique dataset, of unprecedented size, of DCIS, gathered prospectively from many breast units in the UK. It will enable those working in the field to answer some of the questions and address some of the controversies concerning the diagnosis and treatment of DCIS. This can happen only if individuals within breast screening units participate consistently in this national audit. Sincere thanks go to all who are entering and continuing to enter data, ensuring the success of the project.

The remainder of this chapter is adapted from the protocol for the Sloane Project (Version 9, January 2008). The full protocol is available on the Sloane Project web site (www.sloaneproject.co.uk).

3.2 Background and introduction

The NHS Breast Screening Programme (NHSBSP) diagnosed 3159 non-invasive breast cancers in women of all ages during the period 2005–2006.⁵⁰ Prior to the introduction of the screening programme, only 295 cases of ductal carcinoma in situ (DCIS) were recorded in England and Wales in the age band 50–64.⁵¹ The major reason for this marked increase is that the trademark characteristic of microcalcification in the majority of DCIS cases is easily visualised radiologically on a mammogram. Consequently, with the introduction of breast screening, the incidence of this type of cancer has been increasing rapidly, and DCIS now accounts for about 20% of all cancers detected by the NHSBSP.

The invasive potential of DCIS is uncertain and, accordingly, the optimal method of treatment for every case is ambiguous and unclear. The traditional treatment of DCIS is mastectomy, which is more than 95% curative. However, this approach would be extreme in cases in which conservation surgery would suffice. The gap in knowledge is becoming more apparent as a greater number of invasive cancers are being treated, seemingly successfully, with conservation surgery. It remains to be established whether the same treatment can be used for all cases of DCIS because identifying the optimal method of treatment is so difficult.

There are currently some clinical trials of treatment under way. However, making comparisons of treatment options through retrospective audits is difficult due to inherent differences in terms of population included, details recorded and differing interpretations of prognostic parameters (eg how to measure size). Also, the information contained within prospective trials may not evaluate all current treatment practices as they may include only two to four treatment options, none of which may turn out to be the optimal approach.

As a prospective audit recording particular characteristics in terms of radiological and pathological appearance and details of surgical and adjuvant treatment, the Sloane Project aims to compile a database of screen-detected DCIS. At the same time, as a way of maximising this approach, the project will also look at the incidence of lobular carcinoma in situ (lobular in situ neoplasia) and atypical ductal hyperplasia.

The Sloane Project will necessarily be a multidisciplinary project involving all members of the breast cancer multidisciplinary team. The data are collected by way of specifically designed data collection forms, which provide full and detailed information about the patient's journey from diagnosis to treatment. The patients will then be followed up and the incidence of local recurrence, contralateral breast cancer, metastases and death will be determined. Careful prospective collection of these data will enable the correlation of clinical outcomes with treatment received. This information will therefore allow the identification of prognostic indicators and their influence on outcome. As a result, the project will be able to suggest what might be the optimal treatment for DCIS and other non-invasive carcinomas.

3.3 Project design

3.3.1 Outline

The audit aims to collect data from patients in the UK who have non-invasive cancer or atypical hyperplasia detected by screening in the NHSBSP.

3.3.2 *Participating units and data collection*

All UK breast screening units are invited to take part in the audit and submit data. The importance of collecting good quality and complete data cannot be underestimated. The project will rely on this being the case to retain its reliability as a prospective and complete audit. If compliance or failure in data collection does become a problem, this will be highlighted to the screening unit and, if the situation does not then improve, it is likely that the breast screening unit will be excluded from the audit. Units should therefore aim to have a radiologist, pathologist, oncologist and surgeon who are willing to take the lead for their disciplines in their unit's data collection. If some members of the multidisciplinary team are unwilling to take part, completed data from other disciplines will still be accepted.

Each unit will be expected to collect data on all non-invasive breast carcinoma cases detected in their screening unit by the NHSBSP. This will amount to, on average, fewer than one case per week per unit and therefore should not present a significant problem in terms of time and/or effort spent completing the appropriate data collection forms. One method of flagging up those cases that need to be included as 'Sloane' cases will be at the postoperative multidisciplinary team meeting. Another method screening units can use to identify eligible cases is to run a KC62 (this can be done at any time in the screening year) and print off a list of women in columns 27 and 28 of tables A–F2. In addition to this, a further annual cross-check on case completeness will be made by the Sloane Project office.

The individual data will be collected on data collection forms, which have been compiled by the Sloane Project Steering Group. There are separate forms for collecting radiology, pathology, treatment and radiotherapy data. The individual screening units will hold batches of these forms, most of which can be obtained from the Sloane Project office.

There is also a follow up spreadsheet, which will be issued to the Sloane contact on an annual basis. This will assist in the identification of recurrences and contralateral disease. On identification of a recurrence, or diagnosis of contralateral or metastatic disease, a more detailed follow up form will be issued (see section 3.3.9 for more details). The collected data will be sent back to the Sloane Project office for entry into a database, for further analysis and follow up. Feedback will be provided periodically about the ongoing results of the project. An annual summary report will also be produced.

Data collection for the Sloane Project commenced in April 2003. Patients to be included in the audit are all those who have their first offered screening appointment for that screening round on or after 1 April 2003 (ie in line with the KC62 data collection). Data collection will continue to be collected for the foreseeable future and follow up data will also continue to be collected into the future.

3.3.3 *The Sloane contacts*

Each screening unit will need to nominate a lead ‘Sloane contact’ who can deal with any Sloane Project related issues. This will enable the Sloane Project manager to have a focal point to direct any queries or problems that may occur with individual units. Alternatively, the ‘Sloane contact’ can discuss any problems they are encountering individually or within the unit with the Sloane Project manager or the project manager can direct them towards one of the Sloane Project Steering Group members. It is felt that, ideally, a lead clinician would be the best person to be nominated as the ‘Sloane contact’. It can then be left up to this individual to delegate duties as he or she sees fit. It will also be necessary to identify a lead administrative or clerical person to assist in collating and chasing data forms.

3.3.4 *Data collection forms*

- It is essential that the demographic details are filled in at the top of each form to ensure data completeness and quality and to enable analysis and follow up of individual patients.
- The surname and forename boxes are for the individual units’ own information. The forms should be pseudonymised before being returned back to the Sloane Project office. This can be done by crossing out the name boxes with black marker pen. Please cross out only the *name* boxes as the other information will be required to follow up the patients.
- It is therefore essential that the NHS number is filled in, in order that a cross-check between forms can be done and the patients can be easily followed up.
- The Sloane Project office will fill in the ‘Sloane number’ at the bottom of the front page of each form.
- The lead ‘Sloane contact’ for each screening unit should be the person who directs any queries with any aspects of the forms to the Sloane Project manager (contact details provided earlier). If the project manager is unable to answer the query herself, she will consult with the most appropriate person on the Steering Group and provide feedback as soon as possible.
- Requests for further forms should also be directed to the Sloane Project manager.
- The completed forms should be passed back to the lead ‘Sloane contact’ or the individual that he or she has delegated to do this task.
- The completed forms should then be posted back to the Sloane Project office for entry onto the database and analysis.
- The completed forms can be returned individually or as a batch per patient, whichever method is preferred by the ‘Sloane contact’.
- As mentioned earlier, regular feedback will be provided by the Sloane Project manager concerning the ongoing results of the study.

3.3.5 *Radiology data collection form*

- The person who reported the films should complete the radiology form, in full.
- The form is straightforward, involving either tick boxes or figures to be entered into boxes.
- The ‘breast volume’ calculation will be completed at the Sloane Project office, therefore only the two individual measurements

are required ('h' and 'r') from the radiologist/film reader. This measurements were originally labelled 'h' and '2r' on the radiology form but have now been changed to 'a' and 'b' to avoid confusion.

- There are guidance notes available to assist the radiologist with filling in the form.
- For information – the radiology guidelines have been updated since Sloane Project protocol version 7 (June 2003).

3.3.6 Treatment data collection form

- The surgeon performing that specific operation should complete the treatment form, in full.
- If more than two operations are performed, a separate form should be completed for those operations.
- The form is straightforward, involving either tick boxes or figures to be entered into boxes.
- No follow up data are required on this particular form. As mentioned earlier, the Sloane Project manager will issue separate 'follow up' forms on an annual basis.
- If the patient is being referred for radiotherapy then the surgeon will need to inform the oncologist that it is a Sloane Project case. This should be indicated either in the referral letter or with a radiotherapy form attached.

3.3.7 Pathology data collection form

- The pathologist working on that individual's case should complete the pathology form, in full.
- One form should be completed for one episode of non-invasive breast cancer or atypical hyperplasia. A separate form does *not* need to be completed for each specimen; this applies only if the patient has bilateral disease.
- The pathologist will be the most likely person to identify the case as a Sloane case and will be able to flag up any possible 'Sloane Project' cases at the postoperative multidisciplinary team meetings.
- A separate pathology protocol has been produced by Professor Sarah Pinder, with assistance from the Sloane Steering Group pathologists. This provides general and specific specimen handling and reporting guidelines that *must* be adhered to enable the production of minimum dataset information for the pathology section of the Sloane Project. It also provides guidelines for completing the data collection form.
- This 'Sloane pathology protocol' will also be the minimum standard required to be adhered to for anyone participating in the NCRI/BASO UK DCIS Trial (DCIS II) and IBIS II trial and now also forms part of the NHSBSP pathology reporting guidelines.
- The Sloane project manager will be able to collect further non-operative diagnosis information separately at a later date via the screening office computer systems.

3.3.8 Radiotherapy data collection form

- The prescribing oncologist (or therapy radiographer) who has primary responsibility for the patient's radiotherapy treatment should complete the radiotherapy form.
- The form is straightforward, involving either tick boxes or figures to be entered into boxes.
- The oncologist should have been made aware that this is a Sloane

Project case by referral letter from the surgeon. This will not always happen so the oncologists should keep in mind when treating a screen-detected non-invasive breast carcinoma case that it is probably a Sloane Project case.

- The form should be returned to the Sloane Project office on completion of radiotherapy treatment.

3.3.9 *Follow up data collection spreadsheet and form to record recurrence information*

A follow up spreadsheet will be sent out to all 'Sloane contacts' on an annual basis (usually in June or July each year). The spreadsheet will ask for follow up information about all of the patients who should have had at least one follow up appointment since the date they were diagnosed and treated.

The spreadsheet simply asks if the patient has had a recurrence and if she is still alive. If the patient is diagnosed with a local regional recurrence, contralateral disease or metastases, a further more detailed form will need to be completed. This will ask about the diagnosis, treatment and pathology of the recurrence. This form will automatically be issued by the Sloane Project manager on notification of a diagnosis of recurrence.

3.3.10 *Missing data collection*

A missing data spreadsheet will be sent out to each screening unit on an annual basis. This will ask for any professional forms that have not been returned. It will also highlight any missing data items (eg missing demographic information) and will facilitate data completeness and accuracy of the data. It will also assist the screening units in summarising where there are specific problem areas with particular disciplines, enabling them to do an internal check of their data quality. Following on from the issue of this form, missing data and data collection forms are to be returned to the Sloane Project manager as soon as possible.

3.4 **Data collection methods and training**

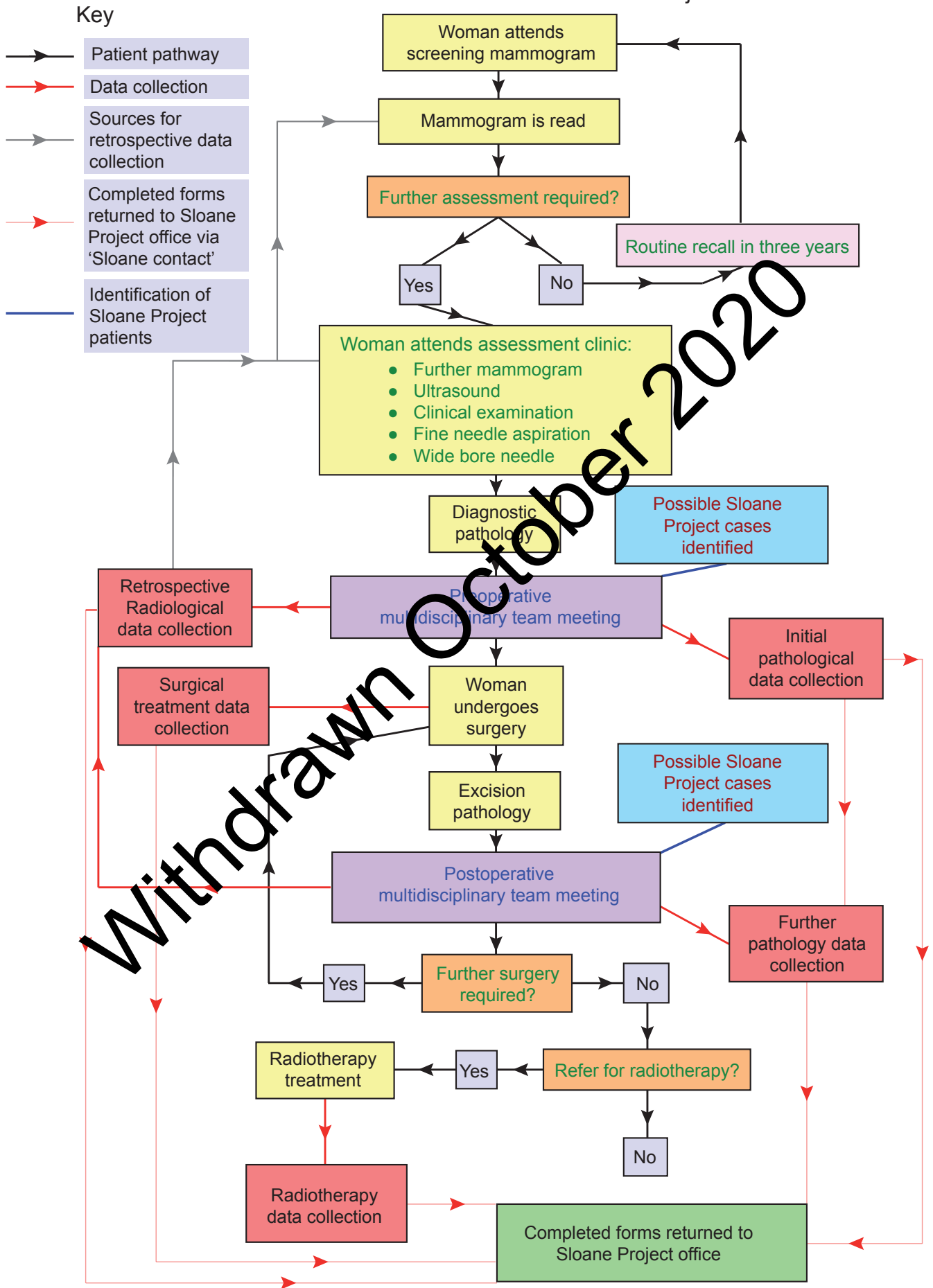
3.4.1 *Data collection methods*

Figure 1 shows a basic flowchart indicating simply the procedures that need to take place for ease of data collection.

The pilot study revealed varying methods of data collection. These are a few examples:

- Sloane Project presentation (general presentation provided on disk in packs, which can be used for this purpose) given at multidisciplinary meeting to make whole team aware. Cases identified at postoperative multidisciplinary meeting. Administrative and clerical person identified to assist with collating forms and returning them to Sloane Project manager.
- Surgeon identifies cases at treatment multidisciplinary meeting and completes treatment form. The completed form is passed on to the radiologist's secretary, who notifies the pathologist of the Sloane case. The radiologist and pathologist complete the forms and the secretary returns the forms to Sloane Project manager.
- Screening centre identifies the cases on a quarterly basis by running

Procedural flowchart for collection of Sloane Project data



the KC62 (as mentioned earlier). Multidisciplinary team coordinator informed of identified cases and is responsible for collecting forms and forwarding them to Sloane Project manager.

As shown, there are various ways that the data can be collected, and this will differ depending on how the different units operate. We would encourage individuality as long as the data are accurate and complete. We would also advise that good communication between team members is a key factor in the successful running of the project in each unit.

Labels are also included in the Sloane Project packs that can be attached to patient case notes to identify them as Sloane Project cases.

3.4.2 Training

A pathology training CD-ROM was originally issued to assist pathologists in classifying the nuclear grade of a specimen. This has now been replaced by a pathology training section on the Sloane Project web site (www.sloaneproject.co.uk). The web site will soon also include a radiology training section. As well as this, various regional pathology training workshops have been undertaken.

3.5 Other issues

3.5.1 Eligibility

Patients are eligible if:

- they have ductal carcinoma in situ (DCIS), lobular in situ neoplasia (LISN) or atypical ductal hyperplasia (ADH) *and*
- their disease was screen-detected within the NHSBSP *and*
- their disease is non-invasive or microinvasive.

Patients are ineligible if:

- they have any invasive disease (however, microinvasion is eligible) *or*
- their disease was not screen detected within the NHSBSP *or*
- their disease was symptomatically detected *or*
- they have recurrent breast cancer.

3.5.2 Consent and ethics committee approval

- Ethics committee approval is not needed for this particular study as it is a prospective audit rather than a trial.
- With regard to the issue of consent, the patient is sent a leaflet before her breast screening appointment indicating, amongst other things, that her records will need to be audited by health service staff. The fact that patients are sent this leaflet in the post and then attend screening indicates that they have 'consented' to having their records audited.
- A letter has been written by the Sloane Project manager, the chair of the audit group and the director of the NHSBSP to cover some of the points with regard to this.

3.5.3 *Analysis of data*

Data analysis will take place at the Sloane Project office. The analysis will examine outcome measures including local recurrence, metastases, contralateral breast cancer development and survival rates. The analysis will also aim to identify prognostic indicators and factors such as the role of margins and adjuvant therapy on outcome. It will also provide detailed information on regional variations in practice.

3.6 **Sloane Project web site**

The Sloane Project web site (www.sloaneproject.co.uk) was launched at the beginning of January 2006. The web site provides useful information about participating in the Sloane Project, as well as downloadable documentation such as the data collection forms, protocols and Sloane Project publications.

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