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Special Paper

The Fourth EORTC DCIS Consensus Meeting (Château Marquette, Heemskerk, The Netherlands, 23–24 January 1998)—Conference Report

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INTRODUCTION

In 1988 [1], 1991 [2] and 1994 [3], the European Organization for Research and Treatment of Cancer (EORTC) gathered experts on all aspects of ductal carcinoma *in situ* (DCIS) from Europe and North America to exchange data, delineate the important issues in this area and reach consensus regarding those issues which have been relatively well-settled and others requiring further investigation. J.A. van Dongen of Amsterdam, The Netherlands, who chaired these three meetings, noted in his introductory remarks to this fourth conference, that the second half of the twentieth century has seen enormous changes in our concepts concerning DCIS. We have moved from an era in which Haagensen defined DCIS as a cancer with 'growth *primarily* in the ducts' associated with a 62% incidence of axillary metastases [4], to one in which DCIS is defined as a cancer *confined* to the ducts, with a potential cure rate approaching 100%. Similarly, DCIS was once a rare curiosity; but in regions where mammographic screening programmes are in place, it now constitutes a substantial proportion of all cases of breast cancer. Our management of DCIS has also undergone revolutionary changes, with an increasing proportion of patients being treated with breast-conserving therapy (BCT).

E.J.Th. Rutgers of Amsterdam, the chair of this fourth conference, described how its organisers decided to focus on two broad topics. First, can we identify subtypes of DCIS that have a low risk of local recurrence when patients are treated with breast conserving surgery without radiotherapy, or, should initial BCT fail, for which the likelihood of developing a potentially life-threatening invasive cancer are small? Second, how can we optimally treat patients with BCT, so as to minimise their risks of recurrence while still attempting to maximise the quality of their lives? This report summarises our deliberations and conclusions.

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LOW-RISK SUBTYPES OF DCIS

H. de Koning of Rotterdam, The Netherlands, began the first day of our meeting by describing how the incidence and epidemeology of DCIS in The Netherlands has changed markedly following the advent of screening programmes. A model of how these changes might affect mortality rates was also presented. These data were complemented by a presentation by L. Holmberg of Uppsala, Sweden of mortality statistics for patients with noninvasive cancer derived from the Swedish National Cancer Registry from 1960–1992. Of note, a case–control study performed on a portion of this population showed that BCT and mastectomy resulted in equal breast cancer specific mortality rates (approximately 6% at 10 years).

These presentations aroused much discussion of how to explain the finding that DCIS forms a lower proportion of cancers found in some European series of screening mammography, compared with those from America. A number of participants felt that criteria for recommending biopsy in the United States are more liberal than those used in Europe. This results in a higher overall biopsy rate and lower specificity, but probably also detects more cases of low-grade DCIS than are found in Europe. There are, however, few data on the ratio of high-grade to low-grade DCIS in screening studies, so this speculation cannot be proven at present. J.L. Peterse of Amsterdam showed that a substantial fraction of patients entered on the EORTC randomised trial (now closed) had low-grade DCIS (39%), but he noted that patients entered on this trial may have been a selected group which is unrepresentative of the entire population of patients with screen-detected DCIS.

Lobular carcinoma *in situ* (LCIS) has traditionally been thought to be a marker of elevated risk of breast cancer development which is roughly equal in the ipsilateral and contralateral breast [5]. This idea has been challenged recently. F. Rank of Copenhagen, Denmark presented data from the Danish Breast Cancer Group registry for 1990–1995

confirming their previous finding showing a predominance of ipsilateral lesions [6]. The National Surgical Adjuvant Breast and Bowel Project (NSABP) has published similar results in a population of patients also followed for about 5 years [7]. A number of participants also felt that the natural histories of atypical ductal hyperplasia (ADH) and atypical lobular hyperplasia (ALH) also remain poorly understood. V. Eusebi of Bologna, Italy noted that a number of pathologists believe that such lesions and low-grade DCIS have similar biologic implications. A proposed classification system, termed 'mammary intra-epithelial neoplasia' (MIN) [8], would unify these entities, while contrasting them to forms of DCIS with much greater potential to cause death. Data supporting such a view from the Van Nuys Breast Group were shown by M.D. Lagios of San Francisco, California, U.S.A. In this study, the risk of developing an ipsilateral invasive cancer following BCT was only slightly higher at 12 years for patients with DCIS of nuclear grade 1 or 2 than the risk for patients with DCIS following diagnostic biopsy. R.R. Millis of London, U.K. described the work of her group showing substantial correlation between the grade of the DCIS component and the grade of the invasive component in patients presenting with infiltrating ductal carcinomas [9]. Other groups have had similar findings [10]. M. van de Vijver of Amsterdam discussed the potential role of biologic markers (such as E-cadherin, HER2 and P53) in aiding classification or in prognosticating the behavior of *in situ* lesions. The participants were particularly interested in the potential of these and other markers to predict response to adjuvant treatments, such as radiotherapy or anti-oestrogens. As yet no clinical data are available regarding this subject.

An important practical issue is whether the patterns or types of calcifications seen mammographically reliably reflect the histologic subtype of DCIS. Presentations by J.H.C.L. Hendriks and R. Holland of Nijmegen, The Netherlands; P. Stomper of Buffalo, New York, U.S.A.; D. Dershaw of New York, New York, U.S.A.; S. Ciatto of Florence, Italy; and M.H. Dilhuydy of Bordeaux, France showed that this is not possible in general [11, 12]. Nevertheless, a very high proportion of patients with linear calcifications (particularly if they are extensive) will be found to have poorly-differentiated DCIS.

Fine-needle aspiration has long been widely used in Europe in the diagnosis of both palpable and impalpable breast lesions. As a result, its advantages and pitfalls are well understood [13, 14] and hence were not reviewed at this meeting. However, core-needle biopsy techniques have not been adopted as rapidly in Europe as in North America. Hence, the participants paid keen attention to reports by D. Dershaw and P. Stomper summarising their institutions' experiences with these devices. When the same radiological criteria were used to recommend core-needle biopsy as were used to recommend open surgical biopsy, the overall number of diagnostic procedures performed remained the same, but fewer of these were open biopsies. This resulted in decreased expense and less trauma to patients. Despite this, core-needle biopsy is not without its own problems. In particular, approximately 25% of patients with only ADH or DCIS found on core-needle biopsy will have DCIS or invasive cancer discovered in the specimen from subsequent open surgical biopsy [15, 16]. The magnitude of this problem may be reduced by the use of vacuum-assisted devices that can obtain larger tissue samples. P.C. Stomper also described the use of core-needle biopsy to obtain samples for DNA flow cytometry and molecular genetic analysis. A potential future problem in using core-needle biopsy may be whether it can accurately distinguish between low-grade, intermediate- and high-grade DCIS; at present, no data are available on this issue.

OPTIMISING TREATMENT TECHNIQUES AND PATIENT SELECTION IN BREAST-CONSERVING THERAPY

Optimising the results achieved with BCT requires accurate determination of the anatomic extent of DCIS in individual patients. R. Holland and J.H.C.L. Hendriks reviewed their data showing that there may be serious discrepancies between the mammographic tumour extent and the pathologic extent [17, 18]. H. Zonderland of Leiden, The Netherlands, discussed the potential of magnetic resonance imaging (MRI) for detecting DCIS and delineating its extent. At present MRI appears to have good sensitivity for detecting DCIS, but its specificity is too low to use it for making treatment decisions without histological confirmation of abnormal findings [19–21]. R. Holland noted that, in preliminary results of a study performed in Nijmegen, MRI detected poorly-differentiated DCIS much more readily than well-differentiated DCIS. Breast MRI technology is rapidly evolving and with time it may become a much more useful tool. However, at present it should not be considered a 'standard' diagnostic tool.

Much attention was also given to the topics of obtaining adequate margins and techniques of pathologic margin assessment. G.F. Schwartz of Philadelphia, Pennsylvania, U.S.A. described the approach his group has taken. After a specimen containing the radiological abnormality is removed, additional specimens (or 'arcs') of tissue several millimetres thick are shaved from around the entire wall of the excision cavity. These are then embedded completely for performing margin assessment. R.W. Blamey and I.O. Ellis of Nottingham, U.K. showed the technique at use in their centre. A cylinder of tissue is taken extending from skin surface (and including skin) down to the pectoralis fascia, centered on the radiological lesion. Oriented intra-operative specimen radiography is used to establish whether re-excision should be performed because of calcifications closely approaching the specimen edge. Margins of the circumferential edge of the cylinder are evaluated by a combination of radially-oriented blocks (for determination of the tumour-free margin width) and circumferentially-oriented blocks. The advantages and disadvantages of these and other approaches were vigorously debated. Numerous participants also discussed the difficulties they had had in interpreting margin status in cases where electrocautery was used.

Only randomised trials can definitively settle issues of optimal patient selection and treatment. Updated results of the NSABP B-17 trial were presented by E. Mamounas of Cleveland, Ohio, U.S.A. [22]. With a mean time on study of 90 months, their trial continues to show that radiotherapy substantially reduced the rates of local recurrence in all patient subgroups. J.P. Julien of Rouen, France described the population entered on the similar EORTC trial, which closed in 1996 after accruing over 1,000 patients. Central review of data sheets and collection of pathology reports and slides for review is proceeding very well, being nearly 85% complete at the time of the meeting. Results divided by treatment arm

have not yet been released by the data monitoring committee; however, they expect that the number of events in the trial will exceed the prospectively-set threshold for this to be done within the year. J. Houghton of London reported that accrual for the U.K. randomised trial has been quite brisk in the past year. At present this study, which investigates the roles both of radiotherapy and tamoxifen, has surpassed its accrual goal for the randomisation between tamoxifen versus none, but has yet to reach its goal for the comparison of excision versus excision plus radiotherapy. Both arms will be kept open until this goal is met, hopefully within the year. Accrual to the Swedish national trial, comparing sector resection alone to resection plus radiotherapy, is also proceeding well according to L. Holmberg; it is also hoped this trial will close shortly. L.J. Solin of Philadelphia described the schemas of two new cooperative group studies in the U.S. A registry study (which he chairs for the Eastern Cooperative Oncology Group) enrolls patients treated with low- or intermediate nuclear-grade noncomedo DCIS of greatest diameter less than 2.5 cm or smaller and high-grade noncomedo lesions 1.0 cm in size or smaller for observation after excision alone, provided that the minimum tumour-free margin width is 3 mm or greater. A randomised intergroup study, to be conducted under the leadership of the Radiation Therapy Oncology Group, comparing surgery alone to surgery plus radiotherapy in similarly-selected patient subgroups, is in an advanced state of preparation and will likely open within the year. Data from two studies examining the effectiveness of tamoxifen in reducing local recurring and reducing the risk of contralateral breast cancer development (the NSABP B-24 trial, now closed and the U.K. trial, noted above) are not yet available.

Retrospective and prospective non-randomised studies have served as the 'pathfinders' in the exploration of DCIS, showing plausible avenues of approach and generating intriguing questions for later investigation by randomised trials. M.J. Silverstein of Van Nuys, California, U.S.A. reviewed and updated his group's experience with the treatment of patients with DCIS with mastectomy, conservative surgery alone and breast conserving surgery plus radiotherapy, which has led to a widely-discussed algorithm for treatment selection (the 'Van Nuys Prognostic Index') [23, 24]. L.J. Solin reviewed the results of an international collaborative study of patients treated with conservative surgery and radiotherapy, whose particular strength lies in its prolonged follow-up [25, 26]. L. Cataliotti of Florence updated his centre's experience [27, 28], which is particularly interesting for showing that the chance of patients having an invasive recurrence following BCT did not depend on the initial grade of the DCIS. U. Chetty of Edinburgh, U.K. briefed the participants on the results achieved in his institution, particularly with regards to time-trends in the presentation of patients and the use of BCT. J.L. Connolly and A. Recht of Boston, Massachusetts, U.S.A. suggested that the key factors which predict the risk of recurrence may differ for patients treated with conservative surgery alone, compared to those treated with surgery plus radiotherapy [29–31]. Schwartz reviewed his experience in treating patients with breast-conserving surgery without radiotherapy [32, 33]. This showed that some patients may take a prolonged time to develop local failure; but, in contradiction to other investigators, he found that only approximately 25% of patients had invasive disease at recurrence. F. Rank spoke about early results from the very large Danish Breast Cancer Group registry of patients treated with either mastectomy or BCT from 1990–1995. Of particular note, recurrence rates following breast-conserving surgery alone in this series (in which wide margin widths were not required) have not depended upon tumour size. R.W. Blamey updated the results achieved in treating patients with DCIS in Nottingham, particularly with regards to the impact of different surgical techniques [34, 35]. They have also found a surprisingly low incidence of contralateral breast cancer development in their population.

In summarising this portion of the meeting, J.L. Peterse pointed out many questions for which few data are yet available. For example, radiotherapy decreases the risk of local failure, but how large are such effects in patients with specific subtypes of DCIS and will this effect be maintained with long-term follow-up? The effects of radiotherapy on cosmetic outcome and the risk of late side-effects (such as carcinogenesis) remain to be determined for this population. How do the cosmetic results of BCT with or without radiotherapy compare to those achieved with mastectomy and reconstructive surgery? Finally, we are beginning to learn about the risks that different subtypes of DCIS have of giving rise to invasive cancers should initial BCT fail, but much of this subject remains uncertain. We also know very little about how patients with DCIS make trade-offs between the increased acute and potential long-term side-effects of radiotherapy and its potential for reducing local (and perhaps distant) recurrence. (Some work along these lines has been done for patients with invasive cancer [36–38].)

Two participants from different sides of the Atlantic were asked to summarise their views on whether it has yet been satisfactorily determined that defined patient subgroups can be routinely treated with breast-conserving surgery without radiotherapy with acceptably low risks of local recurrence. A. Recht noted that most specialists in the United States agree that patients with small, low-grade DCIS which has been widely-enough excised can be treated with surgery alone—but there is *no* consensus on precisely how to define 'small', 'low-grade', or 'widely-enough'. For example, several institutions have shown that microscopic tumour-free margin widths of 10 mm or greater resulted in local recurrence rates of 10% or less following conservative surgery alone [34, 35, 39], but others have had similar results with minimum margin widths of greater than 5 mm [40] or even (in selected patients) of greater than 1 mm [29]. Further, the minimum necessary tumour-free margin width may depend on the histology of the lesion. A. Fourquet of Paris, France emphasised that the NSABP B-17 trial (the only one for which data are yet available) showed that radiotherapy substantially reduced local failure rates in all patient subgroups. While specialist groups have achieved much better results in selected individuals with excision alone than was found by the NSABP, it is not clear that such results can be routinely expected in other institutions. He summarised the excellent results achieved with breast-conserving surgery and radiotherapy in patients treated at the Institut Curie [41]. In an update of the results in patients treated from 1990–1993, he noted that only 2 of 51 patients (including some with focally-involved margins on re-excision) have developed local recurrence with a median follow-up time in the population of 73 months. The actuarial 6-year local failure rate was 2%. Therefore, the current policy of his institution is that 'standard' BCT should include radiotherapy. Prospective studies

are still needed to define subgroups where radiotherapy could be routinely omitted.

E.J.Th. Rutgers outlined ideas and concepts that could be investigated by the EORTC in future prospective studies and randomised trials. These include aspects of surgical therapy (e.g. the need for complete excision of the lesion when adjuvant therapies are used), patient selection and the role of systemic therapies, either as adjuvants to surgery and radiotherapy or as chemopreventative agents. Investigating the role of diagnostic excision alone and anti-oestrogen chemoprevention in patients with low-risk DCIS are particularly attractive strategies.

CONSENSUS OF THE PARTICIPANTS

All these topics were discussed at length (sometimes heatedly) by the participants. A good degree of consensus was reached regarding those issues which are reasonably well understood at present and those for which further research is required before agreement on them can be reached.

The discussions summarising our consensus regarding 'low risk' subtypes of DCIS was led by R.E. Mansel of Cardiff, U.K. and J.P. Sloane of Liverpool, U.K.; those regarding optimal patient selection and management were led by I.S. Fentiman of London, U.K. and J.M. Kurtz of Geneva, Switzerland. Agreement was reached on the following points:

1. The observed incidence of DCIS has increased substantially, largely due to increased detection by screening mammography.
2. There is a high chance (approximately 50%, averaged over all subtypes) that DCIS which has not been completely eradicated will be associated with an invasive breast cancer by the time of clinical recurrence.
3. DCIS accounts for a higher proportion of breast cancers diagnosed by screening mammography in the United States than in the national screening programmes in some European countries (the U.K., The Netherlands and Sweden). This may be due in part to differing thresholds for recommending biopsy, which may lead to 'missing' a number of low-grade DCIS lesions in the latter countries. The truth of these conjectures and, if true, their long-term consequences, must be investigated.
4. Indirect evidence suggests that when DCIS recurs with an invasive component, the grade of the latter is likely to reflect the grade of the initial DCIS. Consequently, a local recurrence resulting from intitial BCT of a low-grade DCIS probably has less lethal potential than that following treatment of a high-grade DCIS. However, further prospective and retrospective studies are needed to confirm this contention.
5. We endorse the reporting of DCIS pathology according to the criteria outlined at the Philadelphia Consensus Conference in April 1997 [42]. All features recommended for recording should be noted (i.e. nuclear grade, necrosis, cellular polarisation, architectural patterns, margin width and degree of involvement, size, relationships of microcalcifications to benign and malignant findings and correlation of pathological findings with specimen radiography and mammography). Neither the Philadelphia conference, nor this gathering, committed themselves to a preferred classification scheme for general use. However, following the Philadelphia guidelines will allow different investigators to continue to use their currently-preferred classification systems while at the same time preserving specific information which will allow them to compare their data with others' results at a later date.
6. The risks of patients dying from breast cancer appear to be numerically similar for ADH, ALH, LCIS and low-grade DCIS. However, if invasive carcinoma later appears, it is more likely to be ipsilateral if the index lesion was low-grade DCIS than if it was one of these other entities. (Note, however, that this concept regarding laterality has been recently challenged).
7. New classification schemes such as MIN, which unify these lesions and contrast them to high-grade DCIS, should be further investigated.
8. Core-needle biopsy, like fine-needle aspiration, reduces the need for open surgical biopsy when the histologic findings are unequivocally benign and correspond to the clinical and radiological features of the case. However, core biopsies which show only ADH may be markers of an underlying DCIS or invasive cancer and should lead to open biopsy. Similarly, invasive cancer may be present when core-needle biopsy shows only DCIS.
9. The characteristics of microcalcifications seen on pre-operative mammograms do not reliably predict histology, except for extensive linear calcifications which are usually associated with high-grade lesions.
10. Molecular pathological studies are scientifically interesting and will likely be important to the classification of DCIS and optimal management of patients in the future. However, at present their exact use is undefined. Hence, there is no clinical requirement to include them in pathology reports.
11. Most women and their physicians prefer BCT to mastectomy for the treatment of DCIS. Hence, we must take measures to optimise the effectiveness of such treatment and to ensure that appropriate patient selection guidelines are used.
12. A critical task in improving the quality of care for patients with DCIS is to standardise pathological terminology so that, even if we are not always speaking the same 'language' to each other, at least we will use the same 'alphabet'.
13. Approximately 20% of patients will have involved microscopic resection margins on the initial attempt at excision, even when performed by experienced surgeons operating in specialised breast units. Improved radiological, surgical and pathological techniques which decrease this proportion should be sought and, when found, adopted widely.
14. The use of electrocautery in BCT is condemned, as it makes adequate pathological evaluation of specimen margins much harder or even impossible.
15. The appropriate follow-up schema for patients treated for DCIS (e.g. frequency of physical examinations and mammography, the use of adjunct diagnostic techniques) must be optimised so as to detect ipsilateral recurrences following BCT or new ipsilateral or contralateral primary breast cancers while they are still highly curable.

16. The consequences of relapse and optimal techniques of salvage therapy (including radiotherapy in previously unirradiated patients) need to be further explored. For example, is there a difference in outcome when local recurrences are managed with further BCT, compared to mastectomy? Should invasive and noninvasive recurrences be managed differently?
17. The risk of relapse following BCT depends predominantly upon microscopic margin width, histologic features and probably tumour size, particularly when radiotherapy is not used. No consensus exists as to *precisely* which subgroups of patients can be treated with surgery alone. Which of these factors are most important in specific patient situations is also not clear. The leaders of the cooperative trial groups present at this meeting agreed that it would be highly desirable to collaborate in order to improve this situation (for example, by interchanging pathologists in order to apply different classification schemes to their materials).
18. Patients with *high-grade* DCIS that is 'extensive' (i.e. a lesion so large or widespread in the breast that performing an oncologically adequate surgical excision will result in an unacceptable cosmetic deformity) should undergo mastectomy. However, there is interest as to whether BCT can be used for patients with extensive *low grade* lesions without facing excessive risks of ultimately developing a fatal invasive breast cancer. The attitudes of patients and physicians to such an approach should be further explored.
19. Adjuvant therapies may allow patients to be treated successfully with BCT who could not be treated well by breast-conserving surgery alone without the use of such wide excision that the resulting cosmetic results would be unacceptable. However, the value of adjuvant therapies depends not only on the magnitude of the residual tumour burden following surgery, but on the evolutionary potential of the lesion and on its responsiveness to such therapy. Further work is needed to assess the conditions under which adjuvant treatments are most effective or ineffective biologically, as well as the absolute reductions in the risk of recurrence that their use affords specific patient subgroups. The decision to use such therapies must balance such benefits against their potential long-term risks.
20. Given the current state of information, further prospective studies and randomised trials are necessary to better care for patients with DCIS. In particular, it would be desirable for the EORTC (alone or in conjunction with other groups) to initiate a randomised intervention trial for patients with low-grade DCIS and a registration study of observation for patients with ADH, ALH, and DCIS following diagnostic biopsy. Pre-entry validation of cases by a panel of expert histopathologists is desirable, given the degree of inconsistency in the classification of these lesions. Details of such efforts will be further considered by the leadership of the EORTC Breast Cancer Group, based on the information and comments made at this conference.

To summarise the current beliefs of the participants at this meeting regarding the management of patients with DCIS (outside of a protocol):

It was generally felt that patients with 'small' lesions (less than 2–3 cm) with 'low-grade' DCIS which is 'widely excised' will be likely to do well following surgery alone; hence, offering such patients a 'wait and see' option is reasonable, provided that careful follow-up is performed. However, there was no consensus as to how to define these terms *precisely* and hence on which subgroups of patients can be adequately treated with surgery alone. Radiotherapy should probably play a more important role in the management of patients with intermediate or high-grade DCIS, although some of these patients may also be adequately treated by surgery alone. Regardless of grade or the planned use of radiotherapy, re-excision should be performed when margins are incompletely excised when cosmetically acceptable. Otherwise, simple mastectomy (with or without immediate reconstruction) may be superior.

CONCLUSIONS

Our knowledge of the natural history and management of DCIS has expanded in ways almost unimaginable at our first meeting nearly 10 years ago. Then, no results from any randomised trials were available; now, we have mature results from one trial, with two others completed and three nearly so. Then, we were able to discuss results from only a handful of retrospective series containing pitifully small numbers of patients with limited follow-up; now, we are almost overwhelmed by the task of keeping up-to-date with the studies performed at a multitude of institutions. Most importantly for our patients, 10 years ago we *hoped* that effective BCT could be offered to the majority of individuals with DCIS; now, we *know* this to be true. We have thus, made great strides in the past decade, astonishing in many ways to those of us fortunate enough to have been at both meetings at the Château Marquette. But we must by no means rest yet—our patients and our consciences demand we do better still in the coming century.

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