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News

Third Meeting of the DCIS Working Party of the EORTC (Fondazione Cini, Isola S. Giorgio, Venezia, 28 February 1994)—Conference Report

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INTRODUCTION

DUCTAL CARCINOMA *in situ* (DCIS) continues to frustrate both clinicians and patients. This poorly-understood disease has been diagnosed more frequently since the previous meetings of the EORTC Working Party in 1988 [1] and 1991 [2]. However, research in Europe and North America has begun to clear away some of the mysteries surrounding DCIS. New classification schemes for DCIS and new approaches to detailed management of patients have been generated. In addition, a revolution is underway in the understanding of molecular mechanisms responsible for the development and evolution of cancer in general, and this will also be of great importance in the understanding of DCIS. These developments coincide with the publication of early results of the first randomised clinical trial to evaluate breast-conserving treatment (BCT) options for patients with DCIS [3]. After a slow start, the European randomised trials, also looking at optimal treatment schedules for DCIS, have begun accruing large numbers of patients, and some of these are likely to be completed soon. Hence, it is timely to reassess our current knowledge of DCIS and to plan new investigations.

OUTSTANDING QUESTIONS

What are the clinical questions that we must answer? Many relate to the possibilities of BCT for DCIS. What patient factors (such as age and menopausal status), tumour factors (such as size and histological subtype) and treatment factors (such as the width of surgical excision and the use of radiotherapy) are critical variables for treatment results [4]? These points were summarised by I. Fentiman (London, U.K.). For example, how can histological subtypes of DCIS be defined so as to have the greatest degree of reproducibility and clinical significance? What is the optimal method of measuring the completeness of excision or, conversely, the volume of the residual tumour burden? And what is the best way to achieve such an excision? Does radiotherapy reduce the long-term risk of local failure? If so, does it have different impacts on the risk of developing invasive and noninvasive disease? What impact does recurrence have on the patient's eventual risk of dying of breast cancer, and what factors (such as the frequency of follow-up visits and mammography) affect the value of salvage therapies?

This meeting focused on those issues now agreed to be most critically important in answering these questions: (1) how to evaluate the distribution of DCIS within the breast and measure reliably the completeness of surgical excision; (2) the subclassification of DCIS; (3) new studies of the basic biology of DCIS; and (4) new findings and updated reports of the retrospective and prospective clinical series that suggest important directions and opportunities for further research. Finally, the participants discussed the promises and pitfalls of continued collaboration, particularly with regards to pooling data from the randomised clinical trials.

EVALUATION OF THE DISTRIBUTION AND COMPLETENESS OF EXCISION OF DCIS

One unresolved question of clinical importance, regarding the spread of DCIS within the breast, is the frequency with which the nipple or nipple areolar complex (NAC) are involved. Dr Duval presented the results of a study from Rouen, France, which found such involvement in the majority of cases. This discrepancy from most other pathological studies, as well as from clinical experience, in which tumour recurrence in the NAC is rare even when local excision without radiotherapy is used, may largely be explained by differences in the size of the lesions studied in these different series. NAC involvement is likely to be frequent only for large tumours (greater than 3–5 cm). Hence, special attention to the NAC is not routinely warranted in patients without frank Paget's disease, except perhaps for lesions in the subareolar region.

Dr Holland and his collaborators in Nijmegen, The Nether-

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lands [5] have performed the most detailed work on distribution of DCIS within the breast. Recently, they attempted to reconstruct the full three-dimensional structure of the spread of DCIS along the ductal tree. In particular, they examined how often such tumours grow without apparent interruption or breaks (continuous growth), how often gaps may appear between areas of DCIS that appear to be within the same ductal tree (discontinuous growth), and how large such gaps may be. Gaps were present in approximately half of the 60 cases reviewed. Most (80%) of these gaps were small (< 5 mm), and of the 20% > 5 mm, only half were > 10 mm. The chance of finding gaps was strongly correlated with the histological type of DCIS. Gaps were more frequent in tumours described as well-differentiated or moderately-differentiated in the newly-proposed draft EORTC classification scheme (see below) than when the tumour was poorly differentiated. In the discussion, several pathologists noted that it is common to see so-called atypical changes between areas of frankly malignant tumours on conventional histological sections that may be responsible for the gaps. Such atypia does not meet the criteria required to diagnose DCIS. This study questions the ability of the pathologist to appreciate the full extent of tumour spread, at least in the well-differentiated type DCIS. In addition, it raises fundamental questions related to how DCIS spreads through the ductal tree: by cell migration or by promoting a "wave" of transformation of adjacent normal or atypical ductal cells or both?

The Nijmegen group has made another important finding. Previously, they reported that the pathological extent of poorly-differentiated DCIS correlated rather well with the radiological extent of the lesion but the mammographic appearance of well-differentiated tumours substantially underestimated their pathological extent. However, when routine mammograms were complemented by magnification views, they detected many more calcifications than could be seen with ordinary techniques, and substantially reduced the discrepancy seen between the pathological and mammographic measurements of tumour extent.

This new information related well to a discussion of the importance of diagnostic mammography and specimen radiography by Dr Ciatto (Florence, Italy). Careful pre-operative mammographic evaluation may be critical in showing otherwise unappreciated areas of tumour spread, thereby increasing the likelihood of obtaining an adequate surgical excision at the first attempt.

Specimen radiography may help in assessing areas requiring further excision intra-operatively. However, most centres obtain only a single radiographic view of the specimen; hence, this allows the assessment of two of the three dimensions of the potential tumour extension. When a second view is obtained along this third axis, often calcifications are noted at the specimen edge. The simplest way to obtain the orthogonal view is to slice the specimen sequentially before obtaining the second specimen X-ray or to prop up the specimen vertically between two blocks of acrylic.

Postbiopsy mammograms, after a 4–6-week period, may also be a valuable tool for assessing the completeness of excision. A recent small series suggests that the presence of residual calcifications usually indicates residual tumour [6]. However, the converse is not true; when postbiopsy mammograms are negative, patients still may have residual disease. Further study of the correlation of findings on postbiopsy mammograms, DCIS subtype and margin assessment is needed to develop the optimal day-to-day management and follow-up of patients.

The most important component of assessing completeness of excision is a meticulous histological examination of the surgical specimen, requiring close collaboration between radiologist, surgeon and pathologist. As outlined by Dr Peterse (Amsterdam, The Netherlands), the surgical specimen must be removed *en bloc*, not in fragments, to allow for marking of the edge prior to histological sectioning. Ideally, the specimen should be oriented with reference to the directions in the breast, so that re-excision efforts may be directed at any involved areas found later. When further excision is considered warranted, due to intra-operative findings (e.g. calcifications found at the edge of a specimen radiograph), subsequent specimens must again be carefully oriented so that a three-dimensional overall impression of tumour distribution can be formed. Extensive sampling of surgical specimens is needed to define tumour size accurately, and the distance of tumour foci from resection margins. Unfortunately, these practices are not always followed. In a central review of cases entered in the EORTC DCIS trial (10853), one-third was inevaluable with respect to completeness of excision.

Although there is consensus on the importance of assessing specimen margins, no agreement has yet emerged on the use of this in selecting treatment options for patients with DCIS. For example, there are few data which correlate the width of the tumour-free margin with the likelihood of finding any residual cancer in the breast following conservative surgery, yet such information seems clearly necessary to decide whether treatment is likely to be successful without the addition of radiotherapy. Dr Silverstein (Van Nuys, California, U.S.A.) has found residual cancer in 45% of patients undergoing re-excision or mastectomy following an initial excision with negative margins (defined as no tumour within 1 mm of the inked specimen edge). In a Swedish study employing a wide (sector) resection without postoperative irradiation, the risk of recurrence was 38% (3/8 patients) when tumour extended histologically within 5 mm of the resection margins, compared to only 6% (2/33) when the width of the microscopically tumour-free margin was greater than 5 mm [7]. Complicating matters further, this critical width may be different for different histological subtypes of DCIS.

Similar concerns relate to the use of margin assessment to select between the options of conservative surgery plus radiotherapy and mastectomy. If radiotherapy is to be used, it is presumed that removal of all the tumour surgically is not necessary; however, experience from BCT invasive breast cancer strongly suggests that the amount of residual tumour burden is related to the risk of local recurrence. In addition, from studies of patients with invasive cancer, it appears that an extensive intraductal component (EIC) indicates a high risk of recurrence unless completely excised [8]. Again, it is likely that different histological subtypes of DCIS will differ with regard to the critical widths of the tumour-free margin (or even the extent of the margin's involvement) compatible with achieving a high rate of local control when radiotherapy is used.

There are insufficient data to state the optimal operational definitions of negative margins. Further work is first needed to correlate the width of the tumour-free margin with the risk of recurrence in patients treated either with excision alone or excision and radiotherapy, particularly with regards to the specific histological subtypes of DCIS. Such information can be obtained, and when used in conjunction with careful pre-operative diagnostic mammography, specimen radiography and postbiospy mammography, this will substantially improve our ability to select the optimal intervention. These requirements place especially great responsibility on the pathologists and

radiologists. Without this, success in the breast-conserving management of patients with DCIS cannot be achieved.

SUBCLASSIFICATION OF DCIS

The biological and histological heterogeneity of DCIS were among the few established facts known at the time of the last meeting of the Working Party [2]. Further work on the immunohistochemical characterisation of these lesions was reviewed by Drs Millis (London, U.K.) and Ellis (Nottingham, U.K.) Despite new approaches of investigating the biology of these lesions, at present, the light-microscopic features of DCIS remain the practical basis for a widely-usable and reproducible working classification of these lesions.

As noted previously, not all subtypes of DCIS will necessarily have the same chance of progressing to an invasive tumour if incompletely excised [2]. As further evidence Dr Eusebi and colleagues in Bologna have confirmed prior studies that missed cancers (i.e. those misidentified as being benign on initial biopsy) may not recur and, if they do progress, the interval before recurrence may be very prolonged. However, this reassuring news was offset by their findings that such recurrences were often invasive, particularly when the original tumour was poorly-differentiated DCIS and could be quite lethal.

These data suggest the importance of accurately distinguishing between DCIS and benign proliferative changes. The most vexing such entity in the differential diagnosis of DCIS is atypical ductal hyperplasia (ADH). There has been considerable interobserver variability in making this distinction, but the use of standardised diagnostic criteria substantially reduced this [9]. Fortunately, the clinical magnitude of this problem has probably been overstated, for most cases of DCIS pose no diagnostic puzzles. In a review of 3 years' experience at the Beth Israel Hospital (Boston, Massachusetts, U.S.A.) Dr Schnitt found that such problem cases formed less than 2% of all breast biopsy cases.

The creation of new, more relevant subclassifications has been one of the most active areas of investigation since our last meeting, both in and outside the EORTC. Several centres used a limited number of features, which they believed to ease assessment and yet adequately reflect the clinical behaviour of the tumour. Three such schemes are of particular interest and were discussed in the meeting at great length.

The oldest of these classifications was that of Dr Lagios (San Francisco, California, U.S.A.) [10, 11]. A simplified version was presented using two variables: nuclear grade and the presence of necrosis. This classification arose from a study of screen-detected patients treated with wide excision alone. It has now been successfully applied in a review of patients with palpable lesions treated with narrow surgical excision and radiotherapy [12] and patients treated variously with wide excision or excision plus radiotherapy (Silverstein, unpublished data).

A second scheme was proposed by Dr Ellis (Nottingham, U.K.), using two features: presence of necrosis and the architecture of the lesion (in particular the presence or absence of the comedo pattern). This scheme has not yet been widely tested clinically, but in a survey of U.K. pathologists, necrosis was the most easily recognised feature of DCIS. The reproducibility of any classification system is obviously critical to its practical usefulness.

At the last Working Party meeting, a Pathology Subcommittee was established to create a single classification scheme to be used to analyse the EORTC trial. Its members have met frequently, and mutually examined specimens to establish uniform diagnostic criteria [13]. The two variables chosen were cytonuclear differentiation, the degree of cytonuclear pleomorphism, and architectural differentiation, the degree to which the tumour cells orient themselves around or toward luminal spaces, that is polarisation of cells.

Although these schemes may seem to be quite different, in practice they are probably not so far apart. If 100 lesions were classified with these three different schemes, it is likely that the number of cases put in each subtype would be very similar. The discussion focused largely on the findings (from prior studies) that strong—though imperfect—correlations are found between the "values" of these particular variables in any given subtype of DCIS. For example, most tumours with extensive intraluminal necrosis also display high nuclear grade, substantial nuclear pleomorphism, comedo architecture and a loss of polarisation; as well as aneuploidy and high growth fractions (see below). Conversely, tumours with micropapillary, clinging or cribriform architecture usually (but not always) have low nuclear grade, little nuclear pleomorphism and little if any necrosis. These constellations or combinations of features are likely to result from underlying genetic abnormalities of which we know little as yet. There is great hope that the light-microscopic appearance of DCIS can be used to predict the behaviour of the lesion following breast conservation therapy. Much work remains to be done before any of these classification schemes can be considered to be superior to another and adopted universally. The predictive value of each scheme needs to be adequately validated, preferably on as many series as possible, and in fact at the meeting, steps were taken towards organising such efforts in conjunction with the clinicians involved in both retrospective and prospective studies. Furthermore, definitions of the histological variables must be clear and be reproducible from one pathologist to another. A scheme which provides improvements in predictive accuracy, but which cannot be used routinely outside a few academic centres or by non-expert pathologists will be of little value compared to a scheme that is slightly less accurate but easy to use.

NEW DEVELOPMENTS IN THE BIOLOGICAL STUDY OF DCIS

Exciting developments in understanding the basic biology of invasive cancer are being extended to the study of DCIS. Several of these were discussed at the meeting.

Angiogenesis is viewed increasingly as a critical factor in tumour growth. In studies conducted by Dr Schnitt and colleagues in Boston (Massachusetts, U.S.A.), two different angiogenic patterns were found associated with many cases of DCIS. Neovascularisation can often be seen diffusely in the stroma surrounding comedo lesions, but is much less frequent in non-comedo DCIS. A minority of cases of DCIS express more limited neovascularisation restricted to the periductal region, termed cuffing. Such neovascularisation has not yet been seen in association with ADH or other benign lesions, although only limited work has been done on these entities. Further, some DCIS produce the angiogenic-inducing factor VPF; up-regulation of the VPF receptor can be demonstrated in the surrounding stromal microvessels.

The problem of contamination of malignant cells by stromal cells limits the study of the genetic alterations occurring in DCIS. However, Dr v.d. Vijver, (Leiden, The Netherlands) reported that more investigations are being performed, mainly using immunohistochemistry but also the polymerase chain reaction. So far, most attention has been directed to alterations in C-*erb*B-2 expression [14] and identifying point mutations in the p53 tumour-suppressor gene [15]. Of interest, none of the

abnormalities seen so far have been specific to DCIS, as opposed to invasive cancer. Indeed, potentially important alterations in the sequence or expression of genes found in invasive cancers have not yet been found in DCIS (e.g. *int2*/cyclin-D1, C-*myc* or the EGF receptor). However, work on many of these genes has only recently begun, and, for technical reasons, some studies are harder to perform in DCIS than in invasive cancers (e.g. finding loss of heterozygosity). Nonetheless, comparison of DCIS to both benign lesions and normal breast tissue and to invasive cancers using new techniques (such as DNA subtraction) may yield substantial progress in our understanding of the processes of transformation and progression in breast cancer.

Dr Andersen (Odense, Denmark) reported poor correlations between the DNA index and nuclear size in DCIS. Heterogeneity within a tumour can also be seen (in an example shown by Dr Lagios) between tumour cells in adjacent terminal ductal-lobular units, and is of particular interest with regards to the developmental biology of invasive cancer, Dr Andersen's laboratory has also found equal DNA profiles in the invasive and non-invasive portions of most predominant DCIS with micro-invasive carcinomas.

Cytogenetic studies of DCIS have not advanced as far as those of invasive lesions. The same chromosomal abnormalities found in invasive cancers have been found not only in DCIS but also in benign proliferative disorders such as fibroadenomas and papillomas. No studies have examined the incidence or type of chromosomal abnormalities that might be found in normal breast tissue. Further work in this rapidly changing field may yield valuable insights into the behaviour of DCIS, and may have important implications for our understanding of the development of cancer in general. The clinical usefulness of such knowledge—for classification, predicting behaviour, and even intervening in the natural history of DCIS—remains to be defined. Nonetheless, the day when the molecular pathologist and the molecular oncologist become members of the team caring for patients with DCIS, may be approaching faster than we realise.

PROGRESS REPORTS FROM NON-RANDOMISED STUDIES AND PROSPECTIVE TRIALS

Many retrospective non-randomised studies have been published or substantially updated or further analysed since our last meeting. Given the biases of patient and treatment selection that such studies are inevitably subject to, they cannot achieve the scientific certainty of a well-designed and conducted randomised clinical trial. Nonetheless, these studies have been invaluable in exploring the terra incognita of DCIS.

Dr Solin presented the results of a collaborative study pooling cases of patients treated with breast conserving surgery and radiotherapy in 10 institutions in Europe and North America [12, 16, 17], and showed that 5-year results substantially understate the eventual risk of local recurrence. Despite a relatively high rate of local failure, the cause-specific survival rate is high. However, salvage treatment is not perfect. One-half of recurrences in this (and other) series were invasive, with some of these latter patients eventually developing metastatic disease. Hence, more work must be done to improve the early detection and management of local recurrences. Dr Silverstein's data [18, 19] confirmed such conclusions.

Several studies have been devoted to attempting to identify patients who can be treated with excision alone with only a low risk of local failure. The results of the San Francisco group strongly suggested that histological subtype will be a critical factor in the results achieved with this approach [10, 11]. Similar findings have recently been published from another American institution [20] as well as in an unpublished study performed in Erlangen, Germany, and presented by Dr Tulusan. However, in one such study from Hamburg, Germany (discussed by Dr Schreer), histological subtype was not found to be a risk factor for recurrence.

One area requiring more extensive investigation is how to categorise and quantify aspects of treatment and patient evaluation. This problem has already been discussed concerning specimen margins. Another important reason why investigators disagree about the interpretations of their finding is the great variation in surgical techniques used. This subject was highlighted by Dr Blamey (Nottingham, U.K.), who gave a detailed description of the approach he and his colleagues have been using in Nottingham since 1988 for tumours of under 4 cm. Their operative procedure was an excision of a full cylinder, including subcutaneous and glandular tissue up to the fascia. They used peroperative specimen radiography to guide removal of further tissue in areas where calcifications approach to less than 1 cm of the resection margin, and performed a re-excision for the approximately 20% of patients in whom DCIS was found to be within 1 cm of the edge of resection microscopically. Because of careful breast reconstruction, the overall cosmetic results were very good, and in 40 patients treated with surgery alone, there were no recurrences, albeit after short follow-up.

Although radiotherapy may lend itself more easily to being measured, nonetheless there remains controversy regarding the optimal treatment techniques and doses to be used in patients with DCIS. Dr Fourquet and Dr Zafrani outlined the current approach at the Institut Curie (Paris, France). Superior results were obtained when a dose of at least 63 Gy was given [21]. The critical level is also governed by the impact of radiation dose on cosmesis. Whether such dosages are still critical is uncertain in an era in which better patient and pathological examinations are performed for screen-detected (rather than palpable) tumours.

Some special types of cancers are so rare that randomised clinical trials of their management will never be practical, even in the co-operative group setting. Paget's disease represents one of such tumours. Dr Rutgers reported on a registration study the EORTC has organised on breast conserving therapy of Paget's disease. With further accrual and follow-up, valuable information is likely to emerge regarding this rare disease.

Finally, Dr Recht illustrated two other problems endemic to clinical research (whether retrospective or prospective) using data from a recent update produced by his colleagues at the Joint Center for Radiation Therapy (JCRT) (Boston, Massachusetts, U.S.A.) [22]. As has been noted, there are substantial differences in patient selection and treatment practices between different institutions. However, such differences may also exist within a single institution, particularly when studies accrue patients over a long period. For example, comparison of patients treated from 1985 and before to those treated from 1986 to 1988 revealed a significant rise in the frequency of re-excision (from uncommon to nearly universal), a similar dramatic increase in the proportion of patients with evaluable specimen margins, and a doubling of the median volume of the excised tissue. The 5-year local recurrence rate in the later patients was much lower than in the earlier cohort. Whether these improvements in management will reduce the 10-year recurrence rate will be seen only after further follow-up. This finding illustrates the dangers of using historical controls to evaluate the results of manipulating one of many changeable parameters.

The second problem illustrated by the JCRT experience is the unexpected appearance of new questions. Recurrence rates differed substantially for patients with or without a family history for breast cancer. This phenomenon has been noted in only one previous series [23]. However, such information has not routinely been gathered in many centres, so it may be very difficult to confirm or deny such findings from existing databases.

Our last report [2] outlined the ongoing and planned randomised trials for patients with DCIS. The first generation of such studies have investigated whether patients can be adequately treated with excision alone or whether radiotherapy must also be used to ensure an acceptable low risk of local failure.

The only one of these trials yet completed is the NSABP B-17 study [3]. Dr Redmond provided updated results. With an average follow-up of 57 months, the 5-year actuarial ipsilateral breast recurrence rates remain nearly identical to those previously published (approximately 10 and 20% with surgery only and with surgery plus radiotherapy arm, respectively). Of note, the reduction in recurrence rates achieved when radiotherapy was employed was proportionally greater for the development of an invasive recurrence compared to non-invasive ones. Review of biopsy material from this study is continuing, so that clinical–pathological correlates of failure should soon be feasible. They are also conducting a central radiological review of mammograms; this is particularly important, as slightly over 80% of the population had non-palpable tumours for which tumour size was previously not determined.

Dr Redmond also touched upon the NSABP B-24 trial, in which patients—all irradiated—are randomised to receive tamoxifen or a placebo for 5 years. This study opened in May 1991. Accrual has been extraordinarily rapid, and they expected to meet their goal of 1800 patients in the spring of 1994.

A long discussion at the meeting focused on whether the B-17 trial had definitively settled the issue of the value of radiotherapy. Most participants were of the opinion that this was not the case. Therefore, none of the European trial groups nor the participants in this consensus meeting felt that the current studies should be closed prematurely.

All the European trials remain to be completed. Some have been progressing relatively on course, but others have not. The first discussed was the Swedish national study, and Dr Ringberg reported that this trial began in southern Sweden only, and has been opened successively in each of the six major health-care districts. Participation has been excellent and accrual had reached nearly half of the planned 1000 cases by late 1993. Now that the trial is open nationwide, completion of accrual should be possible within several years.

Unfortunately, matters have not gone as well in the other Scandinavian countries. The reasons for this reflect the subtle (and not so subtle) differences between the health-care systems and even (for lack of a more exact term) the philosophies of medical decision-making of both patients and doctors among the industrialised countries.

In Denmark, according to Dr Blichert-Toft, only 8% of all patients diagnosed with DCIS since 1990 were entered in their randomised national trial. He and his colleagues still expect to register nearly all patients in the country with DCIS and (because of the efficient centralised Danish cancer registration) to be able to follow them throughout their lives.

In the U.K., first and second generation studies of DCIS were combined in a single trial begun in May 1990. Dr Stewart reported that surgeons can choose to participate in one of two single randomisations, either tamoxifen or radiotherapy (each with or without elective background treatment) or in both randomisations simultaneously. The majority have followed the latter path while none have chosen to randomise for or not for XRT without a background of tamoxifen. After a slow start, accrual had reached nearly half the goal of 1000 patients by October 1993, including roughly one-sixth of the study population being entered by participating hospitals in Australia and New Zealand. The NSABP B-24 study and the U.K. study may provide complementary information on the value of tamoxifen when used in combination with radiotherapy.

Finally, Dr Julien shared a preliminary assessment of patient accrual, characteristics, and overall outcome for the EORTC trial 10853. The pace of accrual has increased rapidly in the past 2–3 years, with nearly 150 patients entered in 1993. Hence, they had reached nearly two thirds of the planned 1000 patients by the time of this conference.

FUTURE DIRECTIONS

With many pieces of the puzzle of DCIS either now in hand or tantalisingly close, enthusiasm among the participants of this meeting for further collaboration and co-operative study has increased beyond that already evident at our last conference. Some already plan to expand efforts to compare rigorously pathological classification systems with one another. In addition, some questions can only be answered by pooling cases. This practice need not be confined to overview analysis of randomised trials. As Dr Miller (Toronto, Canada) observed, one cannot avoid selection bias in even the most careful retrospective (or observational) study, and therefore one cannot achieve the precision of analysis possible with randomised trials. However, the results may be very useful in pointing out phenomena requiring further investigation, quite possibly by a trial.

As noted previously, each study group has collected information in its own way and using its own standards or definitions. While further standardisation of terminology must be done, this is only one of the obstacles in the way of making the most use of our shared resources. Another is the difficulty of gathering new information on past patients when unexpected questions arise. This is particularly difficult in the co-operative group setting, where records are kept in many places (and in many languages!). Problems of data retrieval, validation of the reliability of such data, and cost rapidly become insurmountable when such a feat is attempted for all patients in a study or trial (other than those in relatively small studies conducted at one or a few institutions).

However, as Dr van Dongen proposed, there are ways in which to obtain many of the benefits of such an imposing task at a much lower price in time and effort. This is the nested case–control study. For each patient who develops a recurrence (the case), 2 or 3 control patients are chosen matching the case in those items which are the objectives of the trial as closely as possible (e.g. treatment arm, age). Using previously-agreed standards, data relevant for the risk for treatment failure will then be obtained from hospital records, mammograms, histological slides, or any other relevant source for all cases and controls. Such nested case–control schemes are widely used and accepted in epidemiological studies, including those of suspected carcinogens. They have also been used in some studies of patient outcome. Their methodology, advantages and flaws are by now well understood.

The participants were unanimous in their quick comprehension of the virtues of this approach. More detailed discussions will therefore be held with the study and trial co-ordinators.

CONCLUSION

Despite the widely-varying backgrounds of the participants in this meeting, the very different health-care systems in which they work and their diverse personalities and experiences, a surprisingly high degree of consensus has developed since our last meeting on DCIS. At that time, we could agree only on the major questions that we should ask. We still do not have the answers, but we have come far enough to see their outlines, like the palazzi rising from the fog in the Venetian winter.

We also continue to treat patients with DCIS very differently from one another. One of the major accomplishments of these meetings has been to encourage the exchange and sharing of data, and even investigators, between our groups. Much of what we have learned so far has come from the analysis and comparison of retrospective non-randomised series, and there is yet much that remains to be gained from this approach. Nevertheless, despite our best efforts now and in future to standardise our terminology, definitions and modes of analysis, our diversity is a weakness, as well as a strength. All agree on the importance of completing the current randomised trials and of continuing to use this tool to settle those disputes and answer the new questions that will inevitably arise from our new knowledge.

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Continuing Medical Education: Cardiopulmonary Medicine and Surgery

The Institut Jules Bordet, in conjunction with the Department of Medicine and Surgery of the San Diego School of Medicine, are planning a Continuing Medical Conference on New Approaches to Diagnosis and Treatment in Cardiopulmonary Medicine and Surgery. It will be held between 26 and 28 January 1995 in Coronado, California. For more information, please contact Ms Shirley Kolkey, Course Coordinator, Complete Conference Management, 1660 Hotel Circle North, #220, San Diego, California 92108, U.S.A.; Tel. 619 299 6673; Fax 619 299 6675.

OECI Conference on Cancer and Quality of Life 1995

This conference will be held on 12–14 May 1995 in Bled, Slovenia. It is being organised by the Organization of European Cancer Institutes (OECI), the Institute of Oncology in Ljubljana and Instituto Nazionale per la Ricerca sul Cancro Genova. For further information contact Dr M. Zwitter, Institute of Oncology, 61105 Ljubljana, Slovenia. Tel. 386 61 1314 225; Fax 386 61 1314 180.

Update in Oncology

Update Europe-Society for Medical Education will be holding its "Update in Oncology" congress from 26 to 28 January 1995 in Vienna, Austria. A wide range of topics will be covered including lung and breast cancer, melanoma, principles of radiation therapy, biological response modifiers, and recent developments in hormonal therapy. For more information, please contact Sonja Mak, Mariannengasse 14/11, 1090 Vienna, Austria; Tel. 43 1 405 57 34 13; Fax 43 1 405 57 34 16.