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Breast Cancer Working Conference, 3–6 September 1991, Leuven

Screening and Treatment of Screen-detected Cancer

Anthony B. Miller

IN A plenary lecture, I reviewed the possibilities and limitations of breast cancer screening. In the year since the UICC project concluded that "in women under the age of 50 there is little evidence of a benefit, at least in the first 10 years after initiation of screening" [1] no evidence had accrued to contradict that conclusion, and none was presented at this conference. For women aged 50–69, there is good evidence that screening for breast cancer every 1–3 years can reduce breast cancer mortality [1], approximately a 30–40% reduction commencing about 5 years after the initiation of screening. The challenge now was to obtain the level of effectiveness seen in older women in the research studies in general population programmes. In younger women, there was a need for a major research agenda over the screening–treatment interface, in order to determine why screening was not effective, and how it could be made so. In addition, the evidence accruing from the National Breast Screening Study in Canada suggests that much of the early benefit in older women might be obtained by skilled physical examination. This suggested the need to evaluate physical examination in countries where breast cancer is becoming a more important problem but where available resources do not permit mammography screening.

The tasks emerging in population programmes were discussed by several presenters at other sessions. Thus in a symposium on screen-detected cancer, Sloane emphasised the need for quality pathology. The needs encompass accurate pathological diagnosis and the provision of prognostically significant information as well as high quality cytological services to reduce unnecessary surgical intervention. A national external quality assessment scheme is now in place in the UK with a standard reporting form to ensure consistent collection of similar data using the same terminology. Similar management programmes were also being introduced in the UK for other aspects of screening to ensure adequate quality, These programmes had the additional advantage that they tended to be a prototype of similar programmes for other services that could result in an increase in the overall quality of medical care.

Holmberg attempted to assess whether screen-detected cancers had a different natural history than clinically-detected cancers. Although this question could not be answered for *in situ* cancer, for small invasive cancers, similar receptor content and ploidy supported the supposition that the natural history was similar. Detection when the tumour was small increased therapeutic efficiency, raising the possibility that in many breast cancers metastases occur late in the detectable preclinical phase.

Collette evaluated long-term survival of breast cancers registered during the DOM project in the Netherlands. Survival varied by stage but not by age in women with cancers detected over the age of 50. Screen-detected cancers had longer survival (even after adjustment for lead time). Brekelmans, from the same group, assessed incidence of breast cancer after negative screening. A clear difference was seen between women under and over the age of 50. In the younger women the expected incidence occurred in the second year after an initial screen, in the older women not until year 4. Possible reasons for this were lower sensitivity of the screen or a higher proportion of fast growing tumours in younger women. Evaluation of sensitivity using different durations during which interval cancers were counted as false negatives suggested that a higher proportion of fast growing tumours in younger women was the correct explanation.

In contrast to these presenters who clearly believed that breast cancer screening in women over the age of 50 was appropriate policy, Coebergh from Rotterdam suggested that with breast cancer mortality decreasing as a relative cause of death as women age, there may be less room for a positive effect in terms of absolute increase in longevity, while the costs induced by anxiety, and more complicated management required for screen-detected lesions, meant that previous estimates of cost-effectiveness of breast cancer screening, based largely on the research studies, will be shown to be too optimistic. Some of these assumptions were challenged. For example it was reported that the quality of the new service programmes in the UK exceed those of the preceding research study, while in Sweden, the quality appeared similar to that in the earlier two-county trial. Further, in Nijmegen, the increased costs associated with screening tended to be concentrated on the first (prevalent) round. Afterwards, the programme costs stabilised, with no increased demand for surgical services. Indeed the benign to malignant ratios for biopsies fell below the levels they were before the initiation of the programme. However, a commentator from a district in the UK indicated that there had been unanticipated increased costs accompanying the initiation of screening, that had not been compensated for by increased central funding.

In clinical practice, there is a tendency to concentrate screening on women deemed at increased risk for breast cancer. McKinna described 20 years of experience with such a policy at the Royal Marsden Hospital in London where elevated detection rates were achieved compared with those expected from routine

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screening. Biopsy rates were reduced by a multidisciplinary approach incorporating fine needle aspiration cytology.

Whether or not two views should be used for screening has been assessed by Thurfjell in Uppsala. Two-view screening resulted in lower recall rates, increased referrals for biopsy and higher breast cancer detection. In addition, the same author found that double reading of films increased the detection of small tumours. Although these findings convinced the author that two-view screening with double reading was optimal, on a cost-benefit basis the marginal benefit from the additional view and/or radiologist reading is almost certainly less than the benefit obtained from single-view screening with a single reader.

The extent to which augmentation mammoplasty interferes with mammography screening has been assessed by Silverstein from California. The area of the breast that can be visualised was shown to be reduced, while data on women who developed breast cancer who had had an augmentation mammoplasty suggested detriment compared with women with mammographically detected cancer. However this comparison group can be criticised because of differences in age and because interval cancers in those receiving mammography had not been included.

Leinster *et al.* evaluated the relationship between risk factors for breast cancer and mammographic parenchymal patterns. The strongest relationship was between patterns and body build. With dichotomy of the risk equations there was better prediction for the DY than the P2 pattern. In a poster presentation the same group found evidence that hormone replacement therapy was associated with the P2 parenchymal pattern, i.e. a higher risk category.

de Koning *et al.* have extended their cost-benefit calculations concerning breast cancer screening by factoring in the benefit of preventing advanced breast cancer. As advanced breast cancer results in about 39% reduction in utility for the woman at an average cost for treatment of $21,000, there will be benefits for women and physicians will notice differences in reduction in demand for some treatments. About 47% of the total cost of screening will be reduced by the decreased costs for treatment of advanced disease.

In the poster sessions a number of practical aspects related to breast cancer screening were explored. High compliance following invitations to attend screening was found in new programmes in Finland and Sweden, but lower levels in the west of Scotland and two regions of England, with particularly low levels in one programme in inner London. All programmes appear to have adequate detection rates and to be finding small tumours. Experience with localisation techniques were described from two centres, ultrasound as well as mammography was of value. In one centre adequate pre-operative localisation led to the biopsy often being therapeutic as well as diagnostic. However, in another, the use of mastectomy was not reduced, apparently at least in part by its use for the treatment of duct carcinoma *in situ* (DCIS).

Attempts also continue to find other screening tests. In Austria Rosen *et al.* investigated the validity of a monoclonal antibody against placental ferritin positive T-lymphocytes as a marker of early breast cancer and showed fairly high sensitivity, but at the expense of a specificity level that would be unacceptable for screening.

In the treatment area it was found in the South-East Thames region of England that staging of a number of screen-detected cases was impossible because of surgeon's beliefs that small cancers did not require lymph node examination, or that it was not necessary in post-menopausal women.

Screening can bring to light lesions that are not normally diagnosed in the absence of screening. This is particularly true for DCIS, found by mammography because of calcifications, giving rise to the need for therapeutic protocols to delineate the treatment for these lesions. A nationwide registration scheme in Denmark has suggested that breast conservation is appropriate in these lesions providing adequate post-operative surveillance is continued. An uncontrolled study from France also suggested that conservative treatment was appropriate, though this group gave post-operative radiotherapy. Similar results were reported from series in California, the Netherlands, UK and Italy. It was the impression of most groups that without postoperative radiotherapy local recurrences are unacceptably frequent, though it is unclear whether radiotherapy influences the risk of subsequent invasive cancer and death. Large trials are required to answer such questions. Some trials have been initiated, while in the UK a pilot study of patients with extensive DCIS who decline mastectomy using tamoxifen has been started. In the meantime several groups are using markers of breast cancer progression to identify subgroups of DCIS with more clinical relevance. One study in Nijmegen found 100% of epidermal growth factor receptor positivity in DCIS but only 50% in invasive ductal carcinomas, suggesting that epidermal growth factor is lost upon progression. Similar discrepancies (but at lower positivity levels) were found by the ICRF group in London studying immunohistochemical staining for c-*erb*B-2 protein. DNA flow cytometry measurements of S-phase fraction suggested that rapidly infiltrating tumours were often c-*erb*B-2 negative, possibly due to the fact that the majority of such invasive tumours were derived from the types of DCIS that were themselves negative to c-*erb*B-2. Thus a study in the Netherlands found NEU (c-*erb*B-2) protein overexpression in just under half of cases of DCIS, associated with the comedo-solid growth pattern, large nuclear size, high mitotic rate and poor nuclear grade. It is striking, however, that the numbers of DCIS cases detected in screening programmes are insufficient to account for the invasive cancer rates in such programmes, suggesting that the detectable DCIS lesions are markers of risk, but not precursors of invasive cancer.

In conclusion, the sessions on screening and treatment of screen-detected lesions in this conference showed that many groups are trying to grapple with the myriad of issues that arise as screening moves from research to application in the population. There is a sense of disappointment, however, at the failure so far to demonstrate the value of screening women under the age of 50. Indeed, in a small proportion of breast cancers, the screening-treatment process may be harmful. This creates a challenge that cannot be ignored. What are the biological reasons for this difference between younger and older women? Although in the past it was suggested that lower sensitivity of the screen in younger than older women may be the reason, the high sensitivity and detection rates achieved in the Canadian trial with mammography and good physical examinations and the study reported from Utrecht largely dispell this. It is conceivable that improved therapy for screen-detected cancers using new prognostic markers, recognising that with down-staging achieved by screening conventional wisdom on therapy from clinically detected cancers may no longer apply, could be the answer. However, other suggestions are surfacing, not all formally presented at this conference, that indicate that the process of early diagnosis by mammography could be cutting across biological realities that we are only beginning to perceive. This seems bound to be a very active area of research in the next few

years. In the meantime women who are demanding mammography screening in the 40–49 age group will have to be advised that it is not indicated, though their physicians should remain alert to the possibility of breast cancer developing in this younger age group, and should not hesitate to seek further opinions on those who develop the signs of early breast cancer, with which they should try to become familiar.

1. Miller AB, Chamberlain J, Day NE, Hakama M and Prorok PC. Report on a workshop of the UICC project on evaluation and screening for cancer. *Int J Cancer*, 1990, **46**, 761–769.

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Breast Conserving Therapy: Workshop Report

Ian S. Fentiman

INTRODUCTION

THERE IS agreement now that breast conserving therapy (BCT) is a safe approach for selected patients with operable cancer. The questions that still remain unanswered are how selection should be conducted and whether new techniques can achieve equally good results but with less morbidity and improvement in cosmetic outcome. The workshop considered local relapse after BCT and discussed new approaches to treatment; changing the role of radiotherapy and the use of first-line chemotherapy to render large tumours suitable for BCT.

LOCAL RELAPSE

Three main groups of factors affect local relapse after BCT and relate to patient, tumour and treatment. Of the patient-related factors, young age and small breast size have both been shown to be associated with an increased risk of relapse. A variety of tumour-related factors including type, grade, size, site and nodal status do not appear to alter the risk of local relapse.

Two features strongly correlated with local relapse are extensive intraductal component (EIC) and multifocality. A multifocal tumour was defined by Roland Holland as showing the presence of *in situ* disease or lymphatic invasion more than 1 cm from the infiltrating margins. Multicentric disease, which is rare, was defined as two areas of cancer which are separated by normal glandular tissue.

In a series of 217 mastectomy specimens, serially sectioned, Holland found that 40% of tumours were unifocal and 60% multifocal. Within the multifocal group, 1 in 3 had a very extensive intraductal component. It was suggested that wide excision was necessary to confirm this diagnosis and that such cases might be treated by mastectomy rather than BCT. Peterse also reported that extensive *in situ* component in a biopsy was strongly correlated with residual ductal carcinoma *in situ* (DCIS) in re-excision specimens.

Recht presented data from the Joint Center for Radiation Therapy which concerned EIC, volume of excised specimen and local relapse risk. There was a significant reduction in local relapse in patients with T1 tumour, no EIC and large biopsy volume. Among T2 cases with EIC, a significantly increased relapse rate occurred in those who had a small volume of breast tissue excised.

The Nottingham group have excluded patients with tumours > 3 cm, extensive multifocality or extensive disease from BCT. In addition, those with tumours > 1 cm where vascular invasion was seen, were offered mastectomy. On this basis, only 4/206 (2%) patients treated with BCT developed local relapse after a median follow-up of 18 months.

Kurtz discussed treatment-associated risk factors such as extent of surgery and indicated that local relapse occurred in 10% of patients treated by tumourectomy, against only 4% after quadrantectomy. A future task will be to balance the need for wide excision in some patients with an achievement of a good cosmetic outcome for the majority. Use of the boost may reduce the need for more extensive surgery. The role of the boost is currently being studied in EORTC trial 10882. Optimally, local control should be 90–96% at 5 years and 81–92% at 10 years. Local relapse may be reduced further by either adjuvant endocrine or chemotherapy.

EORTC 10801

The 8 year results of EORTC 10801 were presented by Joop Van Dongen. The trial compared modified radical mastectomy with BCT (tumorectomy, axillary clearance, external radiotherapy 50 Gy and iridium 192 boost 25 Gy). There were 902 women in the trial, of whom 734 (81%) had TNM stage 11 tumours, the remainder having T1 lesions.

The actuarial local relapse free survival at 8 years was 91% for the mastectomy group and 87% for those treated by BCT. No subset differences emerged except that tumour size > 2 cm was a borderline risk factor for relapse in those treated by BCT, but not in the mastectomy group.

It was stressed that the only chance of cure after breast relapse was by salvage surgery consisting at minimum of a total mastectomy, sometimes in association with chest wall resection. Diagnosis of relapse could be difficult and the mean tumour size at the time of relapse was 4 cm. Cytopathology can be helpful in making the diagnosis. The Leiden group presented data suggesting a role for mammography in early detection of relapse using a combination of criteria; developments of new microcalcification and opacities may reduce the size of tumour at the time of diagnosis of relapse.

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