LESSONS FROM A SYMPOSIUM ON BREAST CANCER HELD IN THE COLLEGE ON 25 SEPTEMBER 1998

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Many of the important contributions to the understanding and treatment of breast cancer have been made by European research groups. A symposium was organised to explore some of the salient aspects of the management of this disease by bringing together an international panel of speakers. This report summarises and comments on some of the main messages from this symposium and their impact on clinical practice.

CANCER GENETICS

Taking an accurate family history

Much publicity has been devoted to the clinical implications of the discovery of two cancer-predisposing genes, BRCA1 and BRCA2.[1,2] While the carriage of BRCA1 is known to confer an 80% lifetime risk of developing breast cancer, little is known about the environmental factors which influence the phenotypic expression of the disease. In addition, there are likely to be several other breast cancer predisposing genes as yet unidentified. However, until routine testing for these genes becomes logistically feasible, an accurate complete family history remains the most useful guide to the prediction of genetic risk of mammary malignancy. For example, a woman with an affected first-degree relative under the age of 45 has a 2.2-3.8 times higher relative risk of developing of breast cancer, which rises to a factor of 4 in women with a first-degree relative with bilateral breast cancer. It is important to note that a genetic risk of breast cancer can be transmitted by unaffected individuals and through the paternal line. Three important questions are posed by the cancer geneticist when considering any individual patient:

- What is the chance that there is an abnormal gene in the family?
- What is the chance that the individual patient has inherited the disease?
- If a breast cancer predisposition has been inherited in the family what is the chance that a particular patient will develop it clinically?

Risk depends critically upon age of onset; a patient affected at the age of 30 has a 30% chance of genetic predisposition to breast cancer. If mother and daughter are affected at the age of 30, there is a 90% chance of a genetic defect being detected. This probability falls to 40% by the age of 50 years.

Need for a nationally co-ordinated cancer genetics service

At present, no co-ordinated programme exists of specialist advice in breast cancer genetics for patients and their families. In addition, the laboratory facilities to detect these mutations are distributed unevenly across the country. Only a limited number of centres, for example, have the technical capability to detect mutations of the BRCA1 BRCA2 gene. Furthermore, the failure to detect a mutation in a patient with a significant family history may be due to the genetic defect being missed or to another gene being responsible for the genetic predisposition.

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Organisation of genetic services for breast cancer

Both health care professionals and patients often have a limited awareness of exactly how a cancer genetics clinic operates. Essentially it is a two-stage process. In the first stage, an attempt is made to identify families in whom an abnormal gene is likely to be present and then these families' members are screened for common gene mutations. The second stage involves screening unaffected relatives for the particular abnormal gene identified.

A practical framework for the management of genetic risk in breast cancer is the classification of patients into those with a high or low-moderate risk. No consensus exists in the UK about such a classification and criteria for defining high-risk families vary from centre to centre. However, as an example, using the Cambridge criteria[3] the yield of mutation carriers identified in Cambridge is small. Thus there are many families in which the defective gene(s) are suspected yet in these families no genetic abnormalities are evident on testing.

Management according to level of genetic risk

The management of individual patients should vary according to their degree of risk. Those at high risk (estimated to be 20-40 families per million population) should be seen at specialised cancer genetics clinics linked to breast units. The advantage of this approach is that all women who may be offered genetic testing will be seen by a cancer genetics specialist. For those who carry a mutation, the risk of breast cancer is about 50% by the age of 50; the risk of ovarian cancer is also increased. Those at moderate risk should be managed within breast units without the need to involve the cancer genetics service in most cases. For those individuals who have a family history of breast cancer but do not meet the criteria of moderate risk, the pathway for clinical genetic advice has yet to be agreed. A full explanation is needed, from the patient's GP or consultant breast surgeon/oncologist, of their level of risk and the advantages and disadvantages of breast screening.

The options for management include breast screening, chemoprevention and prophylactic mastectomy. For patients at risk of ovarian cancer the options are regular pelvic ultrasound or prophylactic oophorectomy. Unfortunately prophylactic oophorectomy does not confer absolute protection since, although rare, cancer arising from the mesothelial tissues of the peritoneum has been reported

following resection of histologically normal ovaries.[4]

For families shown to carry a BRCA1 and BRCA2 mutation, screening for the mutation will be offered to family members. It is important that advice is offered by a cancer-geneticist familiar with both the principles of genetics and the management of cancer. Those who have a negative test can be reassured that their risk of breast cancer is no higher than in the normal population. All additional screening which has been established for such a patient, pending the result of the test, will be stopped. It is important that the individuals are made fully aware of the implications and limitations of a negative or positive test before they are tested for any genetic mutation. After the initial interview with the cancer geneticist the patient is given time to think about the implications of having the test. She is offered a second interview with a clinical nurse specialist who reinforces the messages from the first consultation and deals with any queries. Only if the individual agrees to be screened for a genetic mutation is written, witnessed, informed consent obtained. At a subsequent consultation the result is given to the patient face to face with the geneticist, and the implications for further management discussed.

For the moderate risk group (estimated to be about 4,500 women in the UK between the ages of 35 and 49) the risk of developing breast cancer below the age of 50 is three times that of the normal population. Important pointers to its genetic basis are the number of breast cancers in the family, the age of onset and the pattern of other cancers in the family. Those at moderate risk will be offered regular mammography, chemoprevention or prophylactic mastectomy but not genetic testing. The evidence for the usefulness of regular mammography is based on work in Nottingham (Blamey *et al*. - to be published) who showed that in asymptomatic women under the age of 50 who had one first-degree affected relative, the detection rate of breast cancer is about the same as the national breast screening programme from 50-64 years. Based on the Calman-Hine model[5] it is suggested that patients with moderate or low risk are seen at breast unit level. To those at low risk (for example with a mother who has had breast cancer) it needs to be explained that they are at slightly higher risk of developing breast cancer but not that this is sufficiently high to justify mammography below the age of 50. It is clear that most of the burden of explaining the consequences of being in the high, moderate or low-risk category is likely to fall on breast surgeons and clinical or medical oncologists. In addition, it is likely that general practitioners will also have a role in reassuring those who are not considered at any greater risk than the normal population. The resource implications of providing high-quality genetic advice involving specialist cancer genetics clinics, breast units and general practice are likely to be significant. Perhaps each breast unit might consider appointing a surgeon or oncologist to provide advice to general practitioners and channel appropriate referrals of those at high risk to specialist cancer genetics clinics. This might maximise the use of these specialist clinics.

THE PATIENTS' PERSPECTIVE: 'IF YOU HAVENT GOT ALL THE INFORMATION YOU ARE ALL AT SEA'

Communication with patients who are suffering from breast cancer about their management is fraught, not surprisingly, with difficulties. These women harbour fears about death, discomfort and disfigurement. When they attend a consultation, their ability to retain information is often compromised by anxiety. They are often faced with difficult decisions about participation in randomised trials. Good evidence exists that adequacy of information given to patients about treatment options assists their adjustment to the diagnosis of breast cancer; however high levels of anxiety impair the capacity of patients to recall what has been said to them. While the inclusion of patients in randomised trials to evaluate new cancer therapies remains an important NHS priority, levels of recruitment among patients with breast (and other cancers) remain disappointingly low. An important factor may be the information that the doctor gives to the patient about the process of randomisation. Fallowfield *et al*. have shown, in a questionnaire administered to patients with a variety of primary tumour sites, that 76.8% of women would agree to randomisation in a trial comparing two treatments, both of which had been previously explained to be suitable for them.[6] In contrast, when the process of randomisation was compared to tossing a coin, the acceptance rate fell to 44.8%. This rather simplistic analogy might imply to the patient that the doctor was not concerned about them as a person and was devolving the decision on their treatment to an impersonal computer. The use of some form of questionnaire to screen newly-diagnosed patients at the time of their diagnosis with breast cancer would have the benefit of avoiding the attempt to recruit into trials those patients who were opposed to the process of randomisation. It would also enable consultants involved in explaining trials to concentrate their limited time on patients who might consider participation if given adequate information.

ATTITUDES OF SYMPOSIUM PARTICIPANTS TO BREAST SCREENING AND SYSTEMIC THERAPY

Using keypad technology, opinions were sought from the 260 symposium participants on where the effort should, in future, be directed in breast cancer. The opinions of the audience were sought before and after presentations by experts on breast screening and adjuvant systemic therapy. This technology enables us to measure how the opinion of the audience is directly influenced by the presentations of experts. The professions of those who voted were: oncologists (10%), surgeons (16%), nurses (42%) with small numbers of general practitioners, researchers and other personnel. Figures with and without brackets represent the views of the audience to some of the major questions posed before and after the two presentations respectively.

Breast screening

88% [95%] felt that population screening by mammography for women aged 50-64 was worthwhile. For the 50-70 age group, 66% [85%] felt that screening was the most effective method of reducing breast cancer mortality, 18% disagreed and 15% 'did not know'. 58% felt that screening is not equitably delivered across all socio-economic groups. 77%[92%] felt that women older than 65 years should be offered screening.

Systemic therapy

More than 50% [40%] felt that the effect of new treatments on breast cancer cannot improve the survival by more than a few percentage points. 68% [90%] of respondents felt that high-dose chemotherapy was worthwhile. The latter

figure is surprising, because the Dutch randomised trial published shortly before the symposium[7] had shown no apparent benefit of high-dose chemotherapy and associated haematopoetic progenitor cell support over adjuvant therapy with epirubicin, cyclophosphamide and 5-fluorouracil in high-risk women under the age of 60 in whom involvement of the apical node had been demonstrated.[7] However, the results of other trials such as the Anglo-Celtic study[8] addressing the issue of high-dose chemotherapy in the adjuvant setting are still awaited. Testing the views of the audience using the 'digivote system' did show that expert review of the evidence can influence the opinion of participants.

LOCALLY-ADVANCED DISEASE

Locally-advanced breast cancer comprises a heterogeneous group of tumours corresponding to UICC stage III and including T3/ T4, N (any) MO or T (any) N2/3 MO disease. About 15-20% of breast cancers present initially in this category although the incidence seems to be falling. Studies in the 1970s showed that in T4 disease five-year crude survival was only 14% and loco-regional control was 32%.[9] None of these patients received systemic therapy and some received palliative, rather than radical, radiotherapy. Few patients had treatment other than radiotherapy. Better results have been achieved subsequently with radical radiotherapy probably reflecting higher doses of radiotherapy, better fractionation and the use of electron boosts. Systemic therapy certainly seems to downstage disease in about 70% of cases prior to radiotherapy. However, disappointingly, there seems to be very little impact on the long-term local control or survival. The Amsterdam trial compared (a) radiotherapy alone to (b) RT + CMF* (12 cycles) + tamoxifen to (c) continuous tamoxifen + two cycles of adriamycin and vincristine (AV) alternated with two cycles of CMF followed by RT and completed by a further four cycles of AV alternated with CMF.[10] There was no difference in overall or disease-free survival. The Edinburgh trial of four cycles of CHOP† followed by RT compared to radical radiotherapy alone showed a much higher response rate in the combined modality arm but no difference in time to metastatic relapse, survival, disease-free survival or loco-regional control.[11] The EORTC study is the only one to show a survival benefit.[12] It compared radical RT vs RT and hormonal therapy vs RT + chemotherapy + hormonal therapy. Chemotherapy or hormonal therapy both seemed to prolong loco-regional control and delay distant metastasis. The combination of hormonal and chemotherapy is better than either alone. The only group to show a survival benefit was the group treated with RT and hormonal therapy.

New and more effective treatments in the management of locally-advanced disease are still needed. In contrast to early breast cancer, the number of large randomised trials to underpin the benefits of new approaches remain very sparse.

*CMF = cytotoxic combination therapy with cyclophosphamide, methotrexate and 5-fluorouracil.
†CHOP = cytotoxic combination therapy with cyclophosphamide, hydroxydaunomycin (adriamycin), Oncovin (vincristine) and prednisolone.

THE LIMITS OF SURGERY

Breast cancer is increasingly detected by mammography and ultrasound. As a result of this, more and more small non-palpable cancers are being identified. This calls for minimally-invasive surgery. More recently, attempts have been made to select patients for whom the risk of axillary involvement is low and for whom forms of axillary staging less morbid than axillary clearance may be developed.

Local treatment of small tumours

Veronesi's rationale for a quadrantectomy was the excision of the whole ductal tree. The Milan I trial comparing Halsted mastectomy with quadrantectomy + axillary dissection and breast radiotherapy showed no difference in long-term survival.[13] It was not clear, however, whether it was the wide excision or the radical radiotherapy which had contributed to the local control. The Milan II trial compared quadrantectomy for tumours less than 2.5 cm with a less extensive local excision (tumorectomy):[14] both groups received breast irradiation and axillary dissection. The local failure rate was significantly higher in the tumorectomy group (63/345) than in the quadrantectomy group (25/360). In Milan III trial the need for postoperative radiotherapy was evaluated in the same category of patients.[15] They were randomised to quadrantectomy alone or quadrantectomy + breast radiotherapy. In the quadrantectomy alone group radiotherapy was only given at the time of local recurrence. The omission of radiotherapy significantly increased the number of local recurrences. However, again there was no difference in survival. Local recurrence did not compromise survival. Of interest is the observation that in postmenopausal women over the age of 55, who were treated with quadrantectomy alone, the risk of local recurrence is very low (3.8%).

Tumours detected by mammography that are less than 1 cm in diameter carry a risk of axillary node involvement that is very low (4%). For patients with such a low risk, axillary dissection will be carried out with attendant morbidity unnecessarily on 96% of patients. A trial to evaluate axillary irradiation is in progress in Milan on small (<1 cm) screening-detected cancers in which axillary dissection is omitted. All patients are treated by quadrantectomy and breast radiotherapy (QUART), and randomised to receive or not to receive axillary irradiation.

AXILLARY STAGING

Careful pathological assessment of the nodes involved in axillary dissection showed that there was a regular progression of spread from level I to level III in 98.7% of cases, and only in 1.3% were there 'skip' lesions (e.g. involvement of level III, without involvement of levels I and II).[16] These observations established the rationale for examining only one axillary lymph node i.e. the sentinel node. This draining node can be identified by lymphoscintigraphy. The radiopharmaceutical is injected into the primary tumour and the spread of radioactivity tracked by Geiger counter to the sentinel node. The skin is incised over the node and the node removed. Sentinel biopsy was assessed in 361 consecutive cases mainly treated by breast conservation who also underwent subsequent level III axillary dissection.[17] Only one lymph node was found in 67% of the cases and two lymph nodes were found in 26% of cases. Only in four cases was it not possible to identify the sentinel node (1%). The concordance between

a pathologically-positive sentinel node and positive axillary node dissection, and a negative sentinel node and negative axillary dissection, was 96.6%. In 12 cases the sentinel node was negative and the axillary dissection positive (i.e. a false negative of 3%). One limitation is that the 'frozen section' on this lymph node is not completely reliable, i.e. of 128 sentinel nodes reported as negative on frozen section, 23 proved to be positive on subsequent pathological examination. As a result, the technique of frozen section was changed to increase the number of sections from 4-6 to 20-30 sections. This is very labour intensive, requiring three pathologists, and may take 40 minutes during the period of the operation. A trial is underway in Milan in which patients with tumours up to 2 cm are randomised to quadrantectomy, and either axillary node dissection or sentinel node biopsy. It remains to be seen whether results of sentinel node biopsy are translatable from academic units to busy cancer units in district general hospitals. Considerable dedicated logistic support is needed from departments of nuclear medicine and pathology.

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