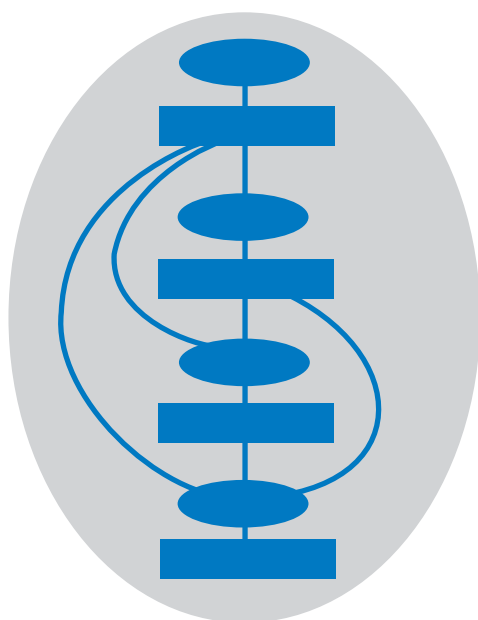


Guidance on Cancer Services

# Improving Outcomes in Breast Cancer

Research Evidence for the Manual Update





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This document is published by CRD on behalf of the National Cancer Guidance Steering Group. It is the companion document to *Improving Outcomes in Breast Cancer: Manual Update* published by NICE, and is part of the Improving Outcomes in Cancer Series.

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YO10 5DD  
UK  
Tel: 01904 433648  
Fax: 01904 432703  
Email: [crdpub@york.ac.uk](mailto:crdpub@york.ac.uk)

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# Contents

Introduction.....	5
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## Topic Areas

1. Primary Care and the Management of Women at High Risk.....	7
2. Patient-Centred Care .....	32
3. Rapid and Accurate Diagnosis.....	37
4. Surgery .....	57
5. Radiotherapy .....	75
6. Systemic Therapy .....	85
7. Follow-Up After Treatment for Early Breast Cancer .....	99
8. Management of Advanced, Recurrent, and Metastatic Disease ...	112

## Appendices

Appendix 1: Analysis of the Potential Economic Impact of Key Areas of the Guidance Update .....	132
Appendix 2: Composition of Research Review and Critical Appraisal Teams.....	156



# Introduction

This document complements and is designed to be read alongside *Guidance on Cancer Services: Improving Outcomes in Breast Cancer – Manual Update*. It provides a condensed version of reviews of the evidence relevant to the updated recommendations made in the manual.<sup>a</sup> The topic areas are dealt with in the same order as in the manual to facilitate cross-referencing.

This document presents a summary of a series of reviews undertaken by researchers at the NHS Centre for Reviews and Dissemination, University of York (see Appendix 2). The review team constructed review questions in consultation with the editorial group and other experts in the field.

Comprehensive searches were carried out for each review question. Where appropriate, strategies were limited by methodology or date. Searches were conducted for each question from a range of databases (Medline, Embase, CancerLit, Cochrane Library, DARE, AMED, HMIC, Cinahl, British Nursing Index, Science Citation Index, Social Science Citation Index). Unpublished data were also identified through personal contact with researchers in the field. Bibliographies of all identified studies were checked for additional relevant studies. The references were imported into Endnote reference management software in order to remove duplicate records and record ordering of articles and reports. The search process was undertaken by Kate Misso (CRD). Full details of the searches and strategies used are available from the NHS Centre for Reviews and Dissemination (tel: 01904 433707 email: nhscrd-info@york.ac.uk).

Searches for existing systematic reviews were completed in July 2000. Searches for primary research studies were completed in July 2001.

Titles and abstracts of all studies identified through electronic searching were screened for relevance by one reviewer. Potentially eligible studies were retrieved in full and one reviewer selected studies. Selection of studies was based on pre-defined inclusion/exclusion criteria that specified for each question the participants, intervention, comparator(s) and outcomes of interest. The same inclusion/exclusion criteria were applied to studies identified from non-electronic sources. Uncertainty was resolved through discussion with another member of the review team. Data were extracted from the included studies by one reviewer and checked for accuracy by another person.

Primary studies were assessed for quality using explicit criteria appropriate to the study design. Existing systematic reviews were included in the review if they met the quality criteria developed for *DARE*.<sup>b</sup>

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a *Guidance for Purchasers: Improving Outcomes in Breast Cancer. The Research Evidence* provides a summary of the reviews relevant to the original manual. It is available from the NHS Responseline on 08701 555 455.

b NHS Centre for Reviews and Dissemination. *Database of Abstracts of Reviews of Effectiveness*. Available from <http://www.york.ac.uk/inst/crd/>

The studies were graded using agreed criteria as outlined in Table 1, which is derived from the CRD guidance.<sup>c</sup> This grading broadly corresponds with the Clinical Outcomes Group categories of evidence used in the original guidance and the update, where A = I or II, B = III, IV, V or VI and C = VII.<sup>d</sup>

**Table 1: Grading of evidence**

Grade	Evidence	
	Diagnosis	Treatment
I	Systematic review of at least level II (below) studies	
II	A blind comparison with reference standard among an appropriate broadly defined consecutive sample of patients	
III	Systematic review of poorer than level II (above) studies	
IV	Any one of the following	<ul style="list-style-type: none"> <li>➤ Narrow population spectrum</li> <li>➤ Differential use of reference standard</li> <li>➤ Reference standard not blind</li> <li>➤ Case control study design</li> </ul>
V	Any two of the following	
VI	Any three or four of the following	
VII	Expert opinion, consensus	
		Quasi-experimental studies (e.g. experimental study without randomisation)
		Controlled observational studies Cohort studies Case control studies
		Observational studies without control groups
		Expert opinion, consensus

The evidence was summarised in a narrative synthesis. The nature of the evidence concerning each question is described and the results summarised along with tables of studies giving fuller details of the research.

This document was prepared by Heather McIntosh, Kate Misso, Jos Kleijnen and Alison Eastwood at the NHS Centre for Reviews and Dissemination, University of York.

c NHS Centre for Reviews and Dissemination. *Report 4 - Undertaking systematic reviews of research on effectiveness: CRD's guidance for carrying out or commissioning reviews*. 2 ed. York: NHS Centre for Reviews and Dissemination, University of York, 2001.

d Mann T. *Clinical Guidelines: using clinical guidelines to improve patient care within the NHS*. London: NHS Executive, 1996.



# Primary Care and the Management of Women at High Risk

## 1. Physical Breast Examination in Primary Care

### The Question

What is the role of routine physical breast examination for self-presenting well women (i.e. asymptomatic) in the primary care setting?

### The Nature of the Research Evidence

No studies were found that reported specifically on the effectiveness of routine physical breast examination in self-presenting well women in the primary care setting. Data on clinical breast examination (CBE) are collected primarily within a different setting, that of screening programmes. Several large studies have explored the relationship between breast self-examination (BSE) among women in the general population and breast cancer mortality.

Data on referral rates of women with breast symptoms from primary to secondary care in the UK, and the appropriateness of these referrals, have been published.

#### **Effectiveness of BSE**

Two large RCTs, a non-randomised trial, two cohort studies and three case-control studies have explored whether breast self-examination (BSE) among asymptomatic women is an effective way to reduce mortality from breast cancer. These studies are summarised in a Canadian systematic review,<sup>1</sup> (Grade I and III). The review is summarised in Table 1b.

#### **Referral rates**

Several UK studies have published data on the presentation rates of breast symptoms in primary care, patterns of referral to secondary care, and subsequent management in secondary care,<sup>2,5</sup> (Grade VI). These studies are summarised in Table 1a.

### Summary of the Research Evidence

Research evidence on the effectiveness of clinical breast examination in self-presenting well women in the primary care setting is lacking. Data from three

large studies that looked at the effectiveness of breast self-examination, and data on referral rates from primary care in the UK, are summarised below.

### **Effectiveness of BSE**

A systematic review that summarised seven studies of the effectiveness of BSE to prevent death from breast cancer found little evidence that BSE is beneficial and concluded that there is more evidence that it can do harm (Grade I and III).<sup>1</sup> The two large RCTs described in the review were conducted in China in 267040 women aged 31 to 64 years, and in Russia in 122471 women aged 40 to 64 years. Although neither trial has yet reached maturity (and the Russian data represent only 62% of all the women who participated in the trial) they have shown no effect of BSE training on breast cancer mortality after five<sup>6</sup> or nine years<sup>7,8</sup> follow up (Grade D). A poorer quality non-randomised trial in women aged 45 to 64 in the UK showed no effect of BSE instruction on breast cancer mortality after 16 years. A cohort study of women aged over 30 years in the USA showed no relationship between self-reported use of BSE among 450156 women and mortality from breast cancer over 13 years (1959 to 1972), no difference was shown in any age group.<sup>9</sup> A poorer quality cohort study in Finland did show lower breast cancer mortality among 29018 respondents who complied with BSE compared to the general population. Three case-control studies found no difference in the self-reported use of BSE between cases and controls. No difference was shown in the stage of breast cancer at diagnosis in either of the RCTs (Grade D). Both RCTs and the non-randomised UK trial, however, reported a higher rate of benign biopsy in the BSE groups (Grade I). The majority of women included in these studies were aged between 40 and 70 years; the review found little evidence specific to younger or older women.

### **Referral rates**

In two UK studies (Grade VI) that reported on patterns of referral of women who presented with a breast abnormality in primary care, referral rates to secondary care were 37% and 55%, but were higher for women over 65 years of age (50% and 73%).<sup>3,4</sup>

Two UK studies have reported on the appropriateness of referral of women with breast symptoms from primary to secondary care (Grade VI). In one study 43/111 (39%) referrals designated as urgent by the GP were considered non-urgent by consultants who reviewed the referral letters, and none of these women had breast cancer. When NHS guidelines were applied to the urgent referral letters, 31 (28%) were inappropriate.<sup>2</sup> In the same study there were 210 non-urgent referrals; 11 of these women had a final diagnosis of breast cancer. According to NHS guidelines 77/210 (37%) did not warrant referral. The authors concluded that rigorous adherence to NHS guidelines would have reduced the total number of referrals from 321 to 213, none of the breast cancer patients would have been excluded, and the number of urgent appointments would have been reduced by 28%. In the other study, surgeons assessed the appropriateness of GP referral of 257 cases and judged that 122 (47%) could have been managed by a GP,<sup>5</sup> (Grade VI).

## 2. Women with a Family History of Breast Cancer

### The Question

Is there any evidence to establish what level of genetic advice and support should best be offered in primary care or specialist cancer genetic services?

This broad issue was addressed as follows:

Who should have access to a hereditary cancer clinic and on what basis should referral from primary care be made?

Who should be offered genetic testing?

What counselling, surveillance, prevention, and prophylactic treatment options should be available for women carrying breast cancer associated gene mutations?

Is there any evidence on risk-benefit and cost-benefit of genetic testing?

### The Nature of the Research Evidence

#### **Who should have access to a hereditary cancer clinic and on what basis should referral from primary care be made?**

A systematic review (Grade III) of the role of primary care in genetic services has contributed to the development of an information pack for primary care on Familial Breast and Ovarian Cancer produced by the Cancer Research Campaign.<sup>10</sup> The pack summarises referral guidelines for GPs.<sup>11</sup> The systematic review is summarised in Table 1b. The UK Cancer Family Study Group has also published preliminary consensus guidelines (Grade VII), regarding genetic predisposition, to help primary care clinicians decide when to refer to a specialist clinic.<sup>12</sup>

Computer support to assist GPs to interpret family histories of breast and ovarian cancer has been assessed using simulated cases,<sup>13, 14</sup> (Grade II, not tabulated).

#### **Who should be offered genetic testing?**

The Trial of Genetic Assessment in Breast Cancer (TRACE) is an RCT of surgical consultation with and without a multidisciplinary genetic assessment service for women with a family history of breast cancer.<sup>15</sup> It was supported by the MRC, Welsh Office and the NHS R&D (Wales), and was designed to provide information of direct relevance to future service provision in relation to genetic aspects of breast cancer. First-stage data, identifying important characteristics of the presenting population, are published.<sup>16</sup> Two other papers are in press, one on psychological aspects. The published TRACE trial data are summarised in Table 1c.

## **What counselling, surveillance, prevention, and prophylactic treatment options should be available for women carrying breast cancer associated gene mutations?**

### Counselling

A pilot study has reported on patient satisfaction with a counselling service programme for hereditary and familial cancers in Amsterdam,<sup>17</sup> (Grade VI, not tabulated).

### Surveillance

There are no published RCTs of mammography surveillance in women at increased risk of breast cancer because of their family history. The British Familial Breast Cancer Group plan to evaluate mammographic surveillance in women under 50 with a significant family history of breast cancer, in terms of breast cancer mortality and cost-effectiveness (HTA Phase II study, protocol). The study proposes to screen a cohort of 20,000 women by regular mammography with a 5-year follow-up.<sup>18</sup>

A Canadian study of surveillance in women at increased risk for breast cancer, referred to a Breast Diagnostic Clinic or a Familial Breast Cancer Clinic, explored the respective roles of mammography, clinical breast examination (CBE) and breast self-examination (BSE) in detecting disease,<sup>19</sup> (Grade VI, not tabulated).

A recent prospective longitudinal study in the Netherlands examined how women who were advised by their GP to undergo surveillance (CBE and mammography) acted on this advice.<sup>20</sup> The GPs were advised on genetic risk assessment by a clinical geneticist, and their compliance with this advice when in turn advising their patients was also assessed (Grade VI, not tabulated).

### Chemoprevention

Chemoprevention has been addressed as a distinct question in this chapter (Primary Care and Referral), see section 3.

### Prophylactic mastectomy

The effect of prophylactic bilateral mastectomy on the incidence of breast cancer among women with a BRCA 1 or 2 mutation was examined in a prospective cohort study in The Netherlands,<sup>21</sup> (Grade V).

The CRC Psychosocial Oncology Group prospective study examined the psychosocial impact of bilateral prophylactic mastectomy for women at increased risk of breast cancer,<sup>22</sup> (Grade IV). A retrospective study (Grade IV) in the US examined the incidence of breast cancer,<sup>23</sup> and long-term satisfaction and psychological and social function<sup>24</sup> following prophylactic mastectomy in women with a family history of breast cancer (moderate and high risk). A small retrospective study in Sweden assessed women's experiences with the decision-making process prior to prophylactic mastectomy and breast reconstruction, their satisfaction with different care givers, and their need for psychosocial support,<sup>25</sup> (Grade VI). These studies are summarised in Table 1c.

Borgen *et al* constructed a US National Prophylactic Mastectomy Registry comprised of a volunteer population of women who had undergone

prophylactic mastectomy, and looked at how many women who had undergone bilateral prophylactic mastectomy later expressed regrets about the procedure.<sup>26</sup>

### **Is there any evidence on risk-benefit and cost-benefit of genetic testing?**

No primary research evidence was identified in the literature, which supports the opinion of experts that nothing has been published on the risk-benefit or cost-benefit of genetic testing (J. MacKay, personal communication).

1

## Summary of the Research Evidence

### **Who should have access to a hereditary cancer clinic and on what basis should referral from primary care be made?**

There is currently no good research evidence to inform which guidelines should be used for referral from primary to secondary care,<sup>12</sup> (Grade VII). A CRC information pack for primary care provides consensus guidelines for GPs (which reflect the consensus views of the Cancer Genetics Group of the British Society of Human Genetics, and was endorsed by the Cancer Genetics Steering Committee)<sup>11</sup> and similar preliminary guidelines have been published by the UK Cancer Family Study Group.<sup>12</sup> Women considered to be at high risk according to current knowledge of genetic risk probabilities should be referred to a genetics/breast clinic for detailed risk assessment (Grade VII).

A systematic review (Grade III) that summarised 51 primary research papers relating to the provision of genetic services in primary care indicated that GPs have limited knowledge about genetics, and although they show general support for a role in primary care it is not clear what that role should be. Information on workload implications of genetics in primary care is limited.<sup>10</sup>

A computer programme, RAGs (Risk Assessment in Genetics), has been designed to categorise risk of breast and ovarian cancer in the primary care setting based on family history. The programme implements detailed referral guidelines and then suggests appropriate management. In a comparative study (Grade II), 36 GPs from Buckinghamshire managed 18 hypothetical simulated cases, six using RAGs, six using Cyrillic (an established programme designed for clinical geneticists), and six using pen and paper (the 18 cases were randomly allocated in to the sets of six).<sup>14</sup> RAGs resulted in significantly more appropriate management decisions (median 6, range 4 to 6) than the other two methods (both median 3, range 0 to 6 for Cyrillic and 0 to 5 for pen and paper). RAGs also resulted in significantly more accurate pedigrees (median 5, range 2 to 6) than Cyrillic (3.5, 0 to 6) or pen and paper (2, 0 to 5). RAGs took 51 seconds longer per case to use than pen and paper, but was not significantly less than Cyrillic. Thirty-three GPs preferred using RAGs overall. This small study of simulated cases on paper may not be representative of all British GPs.

### **Who should be offered genetic testing?**

Evidence to inform recommendations on regional breast cancer genetic testing is lacking at this time.

The TRACE trial in women with a family history of breast cancer has provided evidence on the psychosocial and resource implications of adding individualised genetic assessment, genetic counselling, and gene testing to typical advice and surveillance from a hospital breast clinic. A multidisciplinary assessment service (involving breast surgeons, nurse specialists, and genetics staff) for women with a family history of breast cancer was established to allow a randomised comparison with the existing clinical service. Psychosocial, health economic and service delivery outcomes were evaluated. First-stage data indicated no differences between groups in psychological outcomes, including anxiety, worry and perceived risk of breast cancer (Grade II). The cost of the specialist service model is greater than that of standard care. The authors conclude that there may be little benefit in providing specialist genetic services to all women with a defined family history of breast cancer. Further examination may reveal subgroups of at-risk women who are more likely to experience adverse psychological effects, and others who may improve or remain unchanged.<sup>16</sup> Two further papers have been submitted for publication.

### **What counselling, surveillance, prevention, and prophylactic treatment options should be available for women carrying breast cancer associated gene mutations?**

#### Counselling

Preliminary results from a study of a genetic counselling service indicated generally high levels of satisfaction among 36 women who received counselling at familial cancer clinics in Amsterdam, where multidisciplinary teams care for patients and their family members,<sup>17</sup> (Grade VI). The multidisciplinary team included, among others, an oncology nurse, clinical geneticist, and a molecular pathologist. Overall, 41% (14/34) of respondents reported that they would have liked to have had psychosocial support at least once during the counselling process.

#### Management options

The currently available options for women who are still considered to be at high risk of breast cancer after detailed assessment at a genetics/breast clinic following referral from primary care are (i) early mammography, (ii) participation in research studies (e.g. tamoxifen breast cancer prevention trials), and (iii) prophylactic mastectomy. There is no strong evidence yet regarding the effectiveness of these options.

#### Surveillance

Preliminary results from a Canadian study suggest that surveillance may be useful in detecting breast cancer at an early stage in women at increased risk for breast cancer. The regular performance of mammography, CBE and BSE appeared to be necessary to achieve these results,<sup>19</sup> (Grade VI).

There is currently a lack of consensus on whether surveillance (CBE and mammography) as recommended by the GPs in a prospective study in the Netherlands is effective in women under the age of 50.<sup>20</sup> This study concluded that the value of giving genetic advice in primary care is questionable because women show a low level of compliance with genetic advice from their GP, and

GPs in turn show a low level of compliance with advice from clinical geneticists (Grade VI).

The British Familial Breast Cancer Group evaluation of mammographic surveillance in women under 50 with a family history of breast cancer will not generate data for a number of years.<sup>18</sup>

## Chemoprevention

Chemoprevention has been addressed as a separate question in this chapter (Primary Care and Referral), see section 3.

## Prophylactic mastectomy

A study in The Netherlands (Grade V) looked at the incidence breast cancer among a prospective cohort of women with BRCA 1 or 2 mutations (high risk) who chose either prophylactic bilateral mastectomy or surveillance. Follow-up was short, only three years in both groups, during which no case of invasive breast cancer occurred after prophylactic mastectomy (76 women, 219 women-years at risk), compared to 8 cases among 63 women in the surveillance group (318 woman-years at risk). The potential effect of a change in menopausal status during the study period (natural or oophorectomy) was adjusted for in the analysis, and still a significant protective effect of mastectomy on the incidence of breast cancer was shown ( $P=0.01$ ). The surveillance programme included BSE, CBE, mammography and MRI. However, data on adherence to the surveillance programme are not reported.<sup>21</sup>

A retrospective study (Grade IV) in the US suggested a 90 to 94% reduction in the risk of breast cancer in women defined as being at high risk because of their family history (breast cancer was diagnosed in 3/214 high risk women compared with 156/403 of a control group of their sisters).<sup>23</sup> The calculated reduction in the risk of death from breast cancer was estimated to be between 81 and 94% (95% CIs ranged from 31.4 to 99.2). Among women broadly defined as being at moderate risk, an 89.5% ( $P<0.001$ ) reduction in the incidence of breast cancer after mastectomy was estimated using a model of expected incidence. There were no breast cancer deaths in the moderate risk group compared to a predicted 10.4.

The same study separately reported data on long-term satisfaction and psychological and social function,<sup>24</sup> while the smaller UK CRC Psychosocial Oncology Group prospective study looked at the psychosocial and sexual impact of prophylactic mastectomy over 18 months.<sup>22</sup>

The CRC study reported that women who chose surgery had a higher, and often inflated, perception of their risk of developing breast cancer (Grade IV). Women's anxiety levels decreased significantly post-operatively, whereas anxiety remained high after 18 months among women who declined surgery. For women who chose to have surgery, psychological morbidity decreased by 31% (95% CI 15 to 47%,  $P<0.001$ ) 18 months after surgery ( $n=65$ ), whereas there was no significant decrease among the women who declined surgery.<sup>22</sup> In the US study 74% of women (417/563) reported a decreased level of emotional concern about developing breast cancer following bilateral mastectomy. Favourable effects on emotional stability and stress were felt by 23% ( $n=562$ ) and 28%

(n=557) of women in the US study, whereas negative effects were felt by 9% and 14% respectively,<sup>24</sup> (Grade IV).

The UK study showed no significant change in sexual discomfort or pleasure over the 18 month follow-up period in either women who chose or declined prophylactic mastectomy. In the US study 77% of 554 women reported no change or favourable effects on their sexual relationships, and 23% reported negative effects; 25% (140/558) reported negative effects on their feelings of femininity.

Satisfaction with body appearance was affected in a negative way for 201/559 women (36%) in the US study (95% of the cohort studied had reconstructive surgery with implants). In the UK study the median body image score (4, on a scale of 0 = best, to 30) did not change between 6 and 18 months post-surgery (again most women had reconstruction). A negative effect on self-esteem was reported by 101/559 (18%) in the US study.

In the small Swedish study (Grade VI) all but one of the 15 women interviewed had need of psychological support from their doctors or psychologists. None expressed dissatisfaction with the genetic counselling that they received, but several had difficulty translating the genetic information. Five women did not remember well what had happened at their pre-surgical/reconstruction consultation. No woman regretted her decision to have surgery, although most women felt there had been no other viable option to reduce their risk of breast cancer. After surgery (with reconstruction) 8/10 women maintained pleasure by touch in their breasts.<sup>25</sup>

Borgen *et al* constructed a US National Prophylactic Mastectomy Registry of women who had undergone prophylactic mastectomy and found that 5% (21/370) had regrets about the procedure. The median follow-up was 14.6 years (range 0.2 to 51). Regrets were more common in women with whom discussion about prophylactic mastectomy was initiated by a physician (19/255), compared with women who initiated the discussion themselves (2/108; P <0.05).<sup>26</sup>

### **Is there any evidence on risk-benefit and cost-benefit of genetic testing?**

Despite the logical and ethical arguments for offering genetic testing to women who may be at increased risk of breast cancer because of their family history, there is a lack of multidisciplinary primary research on the risk-benefit and cost-benefit of offering testing. The 1998 Harper report on *Genetics and Cancer Services*, describes the findings of a working group commissioned by the Department of Health to advise on the service implications of advances in cancer genetics. The report highlighted the need for evaluation of services for cancer genetics since current evidence on efficacy is limited.<sup>27</sup>



## 3. Chemoprevention

### The Question

Does tamoxifen, raloxifene or retinoic acid derivatives provide effective chemoprevention against invasive breast cancer among high risk women, and what impact do they have on quality of life?

### The Nature of the Research Evidence

No systematic review was identified. The available evidence comes from several RCTs which are summarised in Table 1c.

1

#### **Tamoxifen**

Chemoprevention of invasive breast cancer with tamoxifen has been addressed by four RCTs (Grade II): NSABP-P1 in the USA;<sup>28, 29</sup> the Italian trial;<sup>30, 31</sup> the Royal Marsden trial in the UK;<sup>32</sup> and an international multicentre trial, IBIS 1.<sup>33</sup> A planned successor trial (IBIS 2) to compare tamoxifen, anastrozole, both or placebo in women at increased risk because of their family history has not yet begun.

#### **Raloxifene**

The Multiple Outcomes of Raloxifene Evaluation (MORE) multicentre trial randomised postmenopausal women with osteoporosis to 3-years treatment with raloxifene or placebo,<sup>34</sup> (Grade II). The occurrence of breast cancer was a secondary outcome measure.

The Study of Raloxifene and Tamoxifen (STAR) trial is currently on-going in the USA. It compares the effectiveness of 5-years raloxifene versus tamoxifen in reducing the incidence of invasive breast cancer, as the primary outcome, in postmenopausal women. Toxic effects of these regimens and their effect on quality of life will also be evaluated.<sup>35</sup>

There is also an on-going Phase II randomised trial of exemestane and raloxifene for chemoprevention of recurrent breast cancer in postmenopausal women with a history of breast cancer.<sup>36</sup>

#### **Fenretinide**

The European Institute of Oncology (EIO) is currently undertaking a trial of a combination of low dose tamoxifen and fenretinide in premenopausal women at increased risk of breast cancer, and another trial to assess whether fenretinide can reduce breast cancer occurrence in post-menopausal women who are users of hormone replacement therapy (HRT) (EIO web site, no references; first trial was referred to by Decensi *et al* <sup>37</sup>).

An Italian trial randomly assigned women with surgically removed stage I breast cancer or DCIS, to 5-years fenretinide or no treatment. The primary end point was the incidence of contralateral breast cancer, <sup>38-39</sup> (Grade II).

# Summary of the Research Evidence

The RCTs are summarised in Table 1c.

## Tamoxifen

The large NSABP-P1 trial (Grade II) in women at risk of breast cancer showed that tamoxifen prevents or at least delays cancer in women at increased risk to such an extent that the trial was stopped earlier than expected.<sup>28</sup> Tamoxifen reduced the risk of invasive breast cancer by 49% (two-sided  $P < 0.00001$ ) compared with placebo. The reduced risk occurred in all age groups: 49 years or younger (44%), 50 to 59 years (51%) and 60 years or older (55%). In women aged 50 years or older tamoxifen was associated with an increased risk of endometrial cancer (RR 4.01, 95% CI 1.70 to 10.90) and of pulmonary embolism (RR 3.19, 95% CI 1.12 to 11.15). The trial also looked at health-related quality of life. Published data covers the baseline and the first 36 months of follow-up of 11,064 women recruited over the first 24 months of the study.<sup>29</sup> The mean number of adverse effects reported was consistently higher in the tamoxifen group and was associated with vasomotor and gynaecological symptoms (including hot flushes and vaginal symptoms). There was a significant increase in the proportion of women on tamoxifen reporting problems of sexual functioning. Weight gain and depression were not increased in frequency in this trial in healthy women.

The overall benefit of tamoxifen shown in the NSABP trial has not been confirmed so far in the European trials. Preliminary findings from the Italian trial<sup>30</sup> show no difference in the incidence of breast cancer between tamoxifen and placebo, although there is a trend towards a beneficial effect of tamoxifen among women on treatment for more than one year ( $P = 0.16$ ). There was a significantly increased risk of vascular events (mainly phlebitis) and hypertriglyceridaemia (correlated with atherosclerosis, the underlying cause of heart disease and stroke) among women on tamoxifen. Interim analysis of the incidence of breast cancer in the UK trial shows no difference between the tamoxifen and placebo groups (RR 1.06 95% CI 0.7 to 1.7,  $P = 0.8$ ),<sup>32</sup> (Grade II).

There is as yet no international consensus on the effectiveness of tamoxifen for chemoprevention of invasive breast cancer. Comparison among the three RCTs is limited by differences in the population of women recruited. The NSABP trial recruited women with a combination of genetic and reproductive risk factors, women in the UK study were those with a family history of breast cancer, and the Italian study recruited hysterectomised women who would be expected to be at lower risk. Follow-up is continuing in the Italian and UK trials.

The international IBIS 1 trial results are expected in January 2003.

## Raloxifene

The MORE trial of the effect of raloxifene on the risk of breast cancer as a secondary outcome in postmenopausal women with osteoporosis, found that the risk of invasive breast cancer was decreased by 76% during treatment with raloxifene compared with placebo (RR 0.24, 95% CI 0.13 to 0.44,  $P < 0.001$ ). Raloxifene increased the risk of thromboembolic disease (RR 3.1 95% CI 1.5 to 6.2) but did not increase the risk of endometrial cancer (RR 0.8 95% CI 0.2 to

2.7),<sup>34</sup> (Grade II). The findings regarding breast cancer from the MORE trial generate a hypothesis that needs to be tested in further trials.

Data from on-going raloxifene chemoprevention trials are not yet available.

Raloxifene is licensed in the UK for the prevention of non-traumatic vertebral fractures in postmenopausal women considered at increased risk of osteoporosis.

### **Fenretinide**

Data are awaited from on-going European trials of a combination of low dose tamoxifen and fenretinide in premenopausal women at increased risk of breast cancer, and of fenretinide to reduce breast cancer occurrence in postmenopausal women who are HRT users.

The authors of the Italian chemoprevention trial of fenretinide in women who have already had breast cancer, emphasise that their data are exploratory and need to be confirmed. Fenretinide treatment for 5 years has not shown any overall effect in preventing second breast malignancy, contralateral or ipsilateral, in women with early breast cancer, compared to no treatment, although there was a possible beneficial effect in premenopausal women,<sup>38-39</sup> (Grade II).



**Table 1a. Primary studies of referral rates in the UK**

Study, country, grade	Aims of study	Setting	Methods	Outcome measures	Results	Comments
BRIDGE Study Group, 1999 <sup>3</sup> UK Grade VI	To gather information about the presentation and management of breast symptoms in primary care.	34 general practices in South Wales with 3 or more partners, from 1995 to 1996.	GPs recorded data from consultations with women aged over 17 in which a new breast symptom was presented.	Presentation and referral rates.	GPs recorded 1020 new presentations of breast symptoms; median = 6.5 per GP per year (range 1.9 to 14.8). The mean age at presentation was 43.5 years (range 18 to 92). Breast lump was the commonest presentation (46.4%).  The average referral rate was 55.3%, and increased with age (49% for women aged 18 to 25 years; 73% for women over 65 years).	This is the first stage of an on-going study.
Laver, 1999 <sup>5</sup> UK Grade VI	To document the time to diagnosis and appropriateness of referral from primary care among women with breast symptoms.	All surgical outpatient clinics at two hospitals in Sheffield, in May and June 1995.	Information on 323 new referrals to the clinics was gathered prospectively. Data collection continued until a woman received a final diagnosis.	Time to diagnosis and appropriateness of referral.	323 women aged 16 to 85 years (mean and median 45 years) were referred from GPs to specialist breast clinics (244/323 women, 75%), general surgical clinics (70 women, 22%), or outreach clinics (3%).  302 women attended their clinic appointment. 66% of referrals were for breast lumps (200/302 women); 22 women referred (7%) had presented to their GP with concern about their family history.  23/302 women referred (8%) had a final diagnosis of cancer; 60% had benign disease, and 33% were normal (99/302). Time to a cancer diagnosis ranged from the first clinic visit to 18 weeks; 18/23 women were diagnosed within 4 weeks.  Surgeons assessed the appropriateness of GP's referral for 257 cases and judged that 122 (47%) could have been managed by a GP.	Study done in conjunction with Newton 1999  The time between referral by a GP and an appointment at a clinic was not reported.
Newton, 1999 <sup>4</sup> UK Grade VI	To identify the consultation rate for breast symptoms in general practice, and describe patterns of referral to secondary care.	82 general practices in Sheffield, from January to July 1995.	Prospective data were collected by 248 GPs from 508 women consulting for breast symptoms.	Number of patients with defined symptoms, management action.	302/508 women consulted for the first time. 80% of these women consulted with a lump (121/302) or pain (122/302); 5/302 initial consultations were women concerned about a family history of breast cancer.  GPs referred 186/508 women (37%).  84/258 (32%) women in the 16 to 39 years age group were referred, compared to 15/30 women aged over 65 years. Women consulting with a lump or a family history were more likely to be referred (67/121 and 2/5 respectively).	A verification exercise suggested that the form of recording used in the study produced a serious underestimation of the target group.

Study, country, grade	Aims of study	Setting	Methods	Outcome measures	Results	Comments
Patel, 2000 <sup>2</sup> UK Grade VI	To assess the number of unnecessary referrals to a specialist breast clinic, with special reference to urgent referrals.	A breast clinic in a surgical unit providing services for the Scottish Breast Screening Programme. Study dates not reported.	A prospective audit of new patient referrals from primary care to a specialist breast clinic.	Total number of referrals, proportion of urgent and non-urgent referrals, proportion of unnecessary referrals (according to NHS guidelines), waiting time for outpatient appointments and outcomes for these patients.	<p>358 consecutive newly-referred symptomatic women attended 14 clinics. 321 were included in the analysis (age 12 to 91 years, median 45). 32/321 women were diagnosed with breast cancer (age 35 to 91 years, median 62).</p> <p>111 referrals were designated as urgent by the GP. 43 (39%) were considered non-urgent by consultants who reviewed the referral letters. 31 (28%) of the urgent referrals were inappropriate when NHS guidelines were applied to the urgent referral letters. 62% of urgent referral were seen within 5 working days.</p> <p>21 (19%) of the urgent referrals had a diagnosis of breast cancer, 90 (81%) had a benign diagnosis. None of the 39% of urgent referrals considered unnecessary by consultants had breast cancer.</p> <p>210 women were non-urgent referrals (including women with no specific designation on the referral letter). 11/210 had a final diagnosis of breast cancer. 55% were seen within 15 working days. According to NHS guidelines 77/210 (37%) did not warrant referral.</p> <p>Rigorous adherence to NHS guidelines would have reduced the total number of referrals from 321 to 213; none of the breast cancer patients would have been excluded; and the number of urgent appointment would have been reduced by 28%.</p>	Reasons for exclusion of 37/358 referred patients were not given



**Table 1b. Primary care and referral: systematic reviews**

Study, grade	Aims of study	Included studies	Outcome measures	Results	Comments
Baxter, 2001 <sup>1</sup> Grade I and III	To evaluate the effectiveness of breast self-examination (BSE).	2 RCTs (n=389511), 1 non-randomised trial (n=236103), 2 cohort studies (n=506333) and 3 case-control studies (n=4402).	The primary outcome was breast cancer mortality; data on stage at diagnosis and harmful effects were also recorded.	An RCT in China in 267040 women aged 31 to 64 years has not shown a reduction in breast cancer mortality at 5 years follow-up between women who received training in BSE and women who did not. Data from 122471 women aged 40 to 64 who participated in a similar RCT in Russia showed no difference in breast cancer mortality after 9 years. A non-randomised trial in women aged 45 to 64 in the UK found no effect of BSE instruction on breast cancer mortality after 16 years. A large cohort study in 450156 women aged over 30 years in the USA found no difference in breast cancer mortality in any age group between women who said they performed BSE and those who said they did not. A poorer quality cohort study in Finland showed lower breast cancer mortality among 29018 respondents who complied with BSE compared to the general population. Three case-control studies found no difference between cases and controls in the self-reported use of BSE.  Stage of breast cancer at diagnosis was reported in both RCTs and no difference was shown.  A higher rate of benign biopsy in the BSE groups was reported in both RCTs and in the non-randomised trial.	Adequate review methodology, possible language bias.  Neither of the RCTs has reached maturity. The Russian data represent only 62% of all the women who participated in that trial.  The review found little evidence specific to women younger than 40 or older than 70 years.
Emery, 1999 <sup>10</sup> Grade III	To review research on the role of primary care in the delivery of genetic services.	51 primary research papers that investigated aspects relating to provision of genetic services in primary care.  Most were qualitative, questionnaire or pilot studies, only 1 was an RCT.	Qualitative synthesis in 5 key areas:  1. GPs knowledge about genetics  2. GPs attitudes towards genetics  3. Current practice in primary care  4. Patient attitudes towards primary care involvement in genetics  5. Delivering genetic services in primary care	Heterogeneity of methods and outcomes precluded pooling the data.  GP knowledge: 10 studies (1989-99; UK, Europe, USA) showed GPs had limited knowledge of genetics.  GP attitudes: 17 studies (1979-99; UK, Europe, USA, Australia) indicated general support for primary care playing a role in genetics; precisely what this role should be was not clear.  Current practice in primary care: information on workload implications of genetics in primary care is limited; increase is anticipated as genetic medicine continues to advance. Use of family history information currently collected in primary care is unclear.  Patients' attitudes: 2 small qualitative studies (UK) of patients from secondary care indicate that patients view the role of the GP as gate-keeper to specialist services.  Delivering genetic services in primary care: useful support strategies for GPs in primary care genetics may derive from on-going RCTs of computer decision support for genetic risk assessment, an educational pack incorporating referral guidelines, and genetic nurse specialist outreach clinics.	Thorough systematic review (contributed to the development of the Cancer Research Campaign information pack for primary care on Familial Breast and Ovarian Cancer).

**Table 1c. Primary studies in women with an increased risk of breast cancer**

Study, country, grade	Aims of study	Participants	Intervention	Outcome measures	Results	Comments
<b>Genetic risk</b>						
Brain, 2000 <sup>16</sup> UK (TRACE) Grade II	To determine the psycho-logical benefits and costs of receiving genetic assessment from a multi-disciplinary genetics clinic.	Women resident in Wales referred by their GP to a breast surgeon at a DGH because of a family history of breast cancer (i.e. having a first-degree female relative diagnosed with breast cancer before 50 years of age, or with bilateral breast cancer at any age, two or more first-degree relatives with breast cancer, or a first and second-degree relative with breast cancer).  545 women, mean age 42 years (range 19 to 73); relatives affected, mean 2 (range 1 to 9).	Trial clinic: a multidisciplinary genetics assessment service (including a clinical geneticist and a genetic nurse specialist), in addition to input from specialist surgical staff (including a breast surgeon and a breast care nurse), surveillance and advice on risk management.  Control clinic: input from specialist surgical staff (including a breast surgeon and a breast care nurse); surveillance and advice on risk management (standard practice).	Women's emotional well-being: general anxiety (State-Trait Anxiety Inventory), Breast cancer worry (Breast Cancer Worries scale); Perceived risk of breast cancer; Knowledge of familial breast cancer; Satisfaction.  Outcomes were measured at baseline, immediately after the clinic and 9 months after the clinic.  Cost and consequences analysis.	General anxiety: difference between groups not statistically significant.  Breast cancer worry: women in both groups experienced statistically significant reductions in anxiety. Difference between groups not statistically significant.  Perceived risk of breast cancer: difference between groups not statistically significant.  Knowledge of familial breast cancer: the trial group had significantly higher knowledge scores immediately after the clinic (P=0.004); there was a significant increase in knowledge in both groups, but the magnitude of the increase was significantly greater in the trial group (P=0.05).  Patient satisfaction: women in both groups found attending the clinics highly satisfying. Difference between groups not statistically significant.  The mean cost of an initial consultation at the specialist genetic clinic was £14.27 (95% CI 12.30 to 16.24) more than routine care (a consultation with a breast surgeon). Total extra cost per originally presenting woman rises to £60.98 with counselling and genetic testing of affected relatives.	An adequately described RCT, allocation concealment not reported. Full details of withdrawals and loss to follow-up were reported





Study, country, grade	Aims of study	Participants	Intervention	Outcome measures	Results	Comments
<b>Prophylactic mastectomy</b>						
Bebbington Hatcher, 2001 <sup>22</sup> UK Grade IV	To investigate the psychosocial impact of bilateral prophylactic mastectomy for women at increased risk of breast cancer.	143 women at increased risk of breast cancer (referred by clinicians) who were offered bilateral prophylactic mastectomy. Median age 38 to 40 years.  79 women chose to have prophylactic mastectomy, 64 declined surgery.	Semi-structured interviews using questionnaires as soon as possible after referral to the study. Women who chose to have prophylactic mastectomy were interviewed again 6 and 18 months post-operatively; women who declined surgery were interviewed again 18 months after the first interview.	Psychological and sexual morbidity.	<p>For women who chose to have surgery, psychological morbidity decreased by 17% (95% CI 2 to 32%, P=0.04) 6 months after surgery (n=71) and by 31% (95% CI 15 to 47%, P&lt;0.001) 18 months after surgery (n=65). There was no significant decrease in women who declined surgery.</p> <p>Compared with normative values, at baseline significantly more women who declined surgery were prone to anxiety than those who had surgery (a difference of 22%, 95% CI 6 to 38%). Women's anxiety levels decreased significantly post-operatively, whereas anxiety remained high after 18 months among women who declined surgery.</p> <p>Sexual discomfort or pleasure did not change significantly over time in either group.</p> <p>Problem focused coping was significantly higher among women who chose surgery, whereas using detachment was significantly higher among women who declined surgery.</p> <p>The median body image score was 4, on a scale from 0 (most positive) to 30, and did not change between 6 and 18 months post-surgery (most women had reconstruction).</p> <p>Women who choose surgery had a higher, often inaccurate, perception of their risk of developing breast cancer.</p>	Prospective study with a control group, not randomised.



Study, country, grade	Aims of study	Participants	Intervention	Outcome measures	Results	Comments
Frost, 2000 <sup>24</sup> USA Grade IV	To evaluate women's long term satisfaction and psychological and social function following prophylactic mastectomy.	572 of the same group of women as studied by Hartmann 1999 (below). 543 women (95%) in the cohort studied had reconstructive surgery (implants).	Bilateral prophylactic mastectomy. Mean follow-up was 14.5 years (minimum 2 years).	Psychological and social consequences of prophylactic mastectomy, satisfaction with prophylactic mastectomy.	74% of women reported a decreased level of emotional concern about developing breast cancer (n=563). Reports of no change, favourable effects, negative effects were as follows: Emotional stability 68%, 23%, 9% (n=562) Stress 58%, 28%, 14% (n=557) Self-esteem 69%, 13%, 18% (n=559) Sexual relationships 73%, 4%, 23% (n=554) Feelings of femininity 67%, 8%, 25% (n=558) Satisfaction with body appearance 48%, 16%, 36% (n=559). 391/562 (70%) of women were satisfied with prophylactic mastectomy, 61 (11%) were neutral, and 110 (19%) were dissatisfied.	Same population as Hartmann 1999. Responses reflect women's experiences of both prophylactic mastectomy and reconstructive surgery, as 95% had both.
Hartmann, 1999 <sup>25</sup> USA Grade IV	To generate reliable data on the outcomes of prophylactic mastectomy in a well-defined cohort of women with a family history of breast cancer.	639 women with a family history of breast cancer who underwent prophylactic mastectomy at the Mayo Clinic between 1960 and 1993. 214 were defined as high risk; 425 as moderate risk (criteria given). A group of sisters of the study group of women at high risk, and an expected incidence model (Gail model, based on women screened annually for 5 years) were used as controls.	Bilateral prophylactic mastectomy. Median follow-up was 14 years (minimum 2 years).	Incidence of breast cancer, risk of death from breast cancer.	Breast cancer was diagnosed in 3/214 high risk women (1.4%) and in 156/403 of their sisters (38.7%). The calculated reduction in the risk of breast cancer was 90 to 94%. In the moderate risk group, the incidence of breast cancer was 4/425 compared to the Gail model prediction of 37.4. The calculated reduction in incidence was 89.5% (P<0.001) after mastectomy. In high risk women, the reduction in the risk of death from breast cancer was 81 to 94% (95% CIs ranged from 31.4 to 99.2) in comparison with the control group of sisters. The actual number of breast cancer deaths was 2 in the high risk group and 90 among the sisters. There were no breast cancer deaths in the moderate risk group compared to a predicted 10.4, giving a risk reduction of 100% (95% CI 70 to 100).	Retrospective study with a control group, not randomised. Moderate risk was defined more broadly than in UK consensus guidelines. Predicted incidence calculations took ascertainment bias into account.



Study, country, grade	Aims of study	Participants	Intervention	Outcome measures	Results	Comments
Josephson, 2000 <sup>25</sup> Sweden Grade VI	To assess women's experiences with the decision-making process prior to prophylactic mastectomy and breast reconstruction, satisfaction with different care givers, and need for psychosocial support.	15 women with an expected lifetime risk of developing breast/ovarian cancer of more than 20%, who had prophylactic mastectomy and immediate breast reconstruction between the ages of 29 and 50 years.	Prophylactic mastectomy and immediate breast reconstruction.  The time between surgery and interview ranged from 7 months to more than 3 years.	Experience with factual information and psychosocial support, opinions of prophylactic mastectomy and breast reconstruction.	None of the women expressed dissatisfaction with the genetic counselling that they received, but several had difficulty translating the genetic information. 10 women said that they lacked psychological support at this stage.  5 women wanted more information from the surgical/reconstruction team; 9 were satisfied with the psychological support, and 6 felt no need for it. 5 women did not remember well what had happened at their pre-surgical consultation.  All but one woman had need of psychological support from their doctors or psychologists.  No women regretted their decision to have surgery, although most felt there had been no other viable option. Their priority was to reduce their risk of breast cancer.  After surgery 8/10 women maintained pleasure by touch in their breasts. 5/13 women felt that the surgery changed their relationship with their spouse.	A small, retrospective study with no control group, that used semi-structured interviews.
Meijers-Heijboer, 2001 <sup>21</sup> The Netherlands Grade V	To investigate the efficacy of prophylactic mastectomy in women with a BRCA 1 or 2 mutation.	139 women with a BRCA 1 or 2 mutation who were being monitored for breast cancer because of a familial clustering of breast or ovarian cancer or both.	76/139 women chose to undergo prophylactic bilateral mastectomy and 63 chose to remain under regular surveillance (BSE, CBE, mammography, MRI; US ± FNA where indicated).	The primary outcome was the Incidence of breast cancer.  Women-years at risk from breast cancer, and the number of breast cancers expected was calculated.	No case of invasive breast cancer was observed during 219 women-years at risk following prophylactic mastectomy, compared to 8 cases during 318 women-years at risk in the surveillance group (yearly incidence 2.5%).  The 5-year risk of breast cancer among women in this study was estimated to be 24±9%.  Mastectomy significantly reduced the incidence of breast cancer (P=0.003) HR 0, 95% CI 0 to 0.36. After adjustment for the potential effect of a change in menopausal status, the protective effect of mastectomy remained statistically significant (P=0.01).	Prospective cohort study. Began January 1992, to the end of follow-up in March 2001.

Study, country, grade	Aims of study	Participants	Intervention	Outcome measures	Results	Comments
<b>Chemoprevention</b>						
Cummings, 1999 <sup>34</sup> USA (MORE Trial) Grade II	To determine whether women taking raloxifene have a lower risk of invasive breast cancer.	7705 postmenopausal women with osteoporosis; younger than 81 years (mean 66.5); no history of breast cancer, invasive endometrial cancer, or stroke or venous thromboembolic disease in past 10 years; not taking oestrogen, as defined by the investigators.	Raloxifene 60 or 120mg/day or placebo for 3 years.	The primary outcome was the risk of fracture. The incidence of invasive breast cancer was a secondary outcome.  Endometrial effects.  Adverse effects, including the incidence of pulmonary embolism and DVT were also assessed.	The risk of invasive breast cancer was decreased by 76% with raloxifene (RR 0.24, 95% CI 0.13 to 0.44; P<0.001).  Raloxifene decreased the risk of ER positive invasive breast cancer by 90% (RR 0.10, 95% CI 0.04 to 0.24) but not ER negative invasive breast cancer (RR 0.88, 95% CI 0.26 to 3.0).  Raloxifene did not increase the risk of endometrial cancer (RR 0.8, 95% CI 0.2 to 2.7).  Raloxifene increased the risk of venous thromboembolic events (DVT or pulmonary embolism) RR 3.1, 95% CI 1.5 to 6.2. There was no significant difference between 60 and 120mg/day raloxifene.	A double-blind multicentre RCT, allocation concealment not reported.  Loss to follow-up at 3-years: Raloxifene 22%; Placebo 25%.



Study, country, grade	Aims of study	Participants	Intervention	Outcome measures	Results	Comments
Fisher, 1998 <sup>28, 29</sup> USA (NSABP P-1 trial) Grade II	To evaluate tamoxifen for the prevention of breast cancer in women considered to be at increased risk.	13,388 women at risk of breast cancer i.e. aged 60 or older, or, 35 to 59 years with a 5-year predicted risk of breast cancer of at least 1.66% or a history of LCIS (non-invasive lesion); no clinical sign of breast cancer on physical exam or mammogram in last 180 days; normal blood, hepatic, renal tests; undergone endometrial sampling; not pregnant; no oestrogen or progesterone replacement therapy, no oral contraception or androgens in the previous 3 months; no history of DVT or pulmonary embolism.	Tamoxifen 20mg/day or placebo for 5 years.	The incidence of invasive and non-invasive breast cancer was the primary outcome.  Quality of life: Center for Epidemiological Studies-Depression Scale (CES-D); Medical Outcomes Study Health Status Survey (MOS SF-36); sexual functioning scale; symptom checklist.  Adverse effects.	Median follow-up 54.6 months.  Tamoxifen reduced the risk of invasive breast cancer by 49% (two-sided P<0.00001). Risk was reduced in women aged 49 years or younger (44%), 50 to 59 years (51%), 60 years or older (55%), women with a history of LCIS (56%) or atypical hyperplasia (86%).  Tamoxifen reduced the risk of non-invasive breast cancer by 50% (two-sided P<0.002).  Tamoxifen reduced the occurrence of ER positive tumors by 69%, but no difference was shown in the occurrence of ER negative tumors.  The rate of endometrial cancer was increased with tamoxifen (risk ratio 2.53, 95% CI 1.35 to 4.97).  The rates of pulmonary embolism (RR 3.01, 95% 1.15 to 9.27), stroke (RR 1.59, 95% CI 0.93 to 2.77) and DVT (RR 1.60, 95% CI 0.91 to 2.86) increased with tamoxifen.  Quality of life (baseline and first 36 months of follow-up of 11,064 women recruited over the first 24 months): No difference was shown in clinically significant level of depression scores (CES-D) or physical and mental scores (MOS SF-36). Mean number of symptoms reported was consistently higher with tamoxifen and was associated with vasomotor and gynaecologic symptoms. Significant increase in the proportion of women on tamoxifen reporting problems of sexual functioning	A double-blind RCT, adequate concealment of allocation.  1.6% lost to follow-up were not included in the analysis.

Study, country, grade	Aims of study	Participants	Intervention	Outcome measures	Results	Comments
Powles, 1998 <sup>32</sup> UK (Royal Marsden Trial) Grade II	To evaluate tamoxifen for chemoprevention of breast cancer in women at increased risk because of their family history.	2494 healthy women volunteers at increased risk of breast cancer because of family history; aged 30 to 70 years; no evidence of breast cancer; no history of any cancer, DVT or pulmonary embolism; HRT was allowed.	Tamoxifen 20mg/day or placebo for up to 8 years.	The incidence of breast cancer was the primary outcome. Toxicity, compliance.	Interim analysis; median follow-up 70 months. No difference in the incidence of breast cancer between tamoxifen (34 cases) and placebo (36 cases) RR 1.06, 95% CI 0.7 to 1.7 (P=0.8). 8/70 cancers were non-invasive DCIS, 4 in each group. No apparent interaction between the use of HRT and any effect of tamoxifen on breast cancer occurrence. No significant difference in other cancers, DVT, pulmonary embolism, or non-breast cancer deaths. Accuracy for volunteered history of compliance estimated to be 96% based on blood testing.	An interim analysis of a double-blind RCT with adequate concealment of allocation. Exclusions less than 1% in each group.
Veronesi, 1998 <sup>30</sup> Italy Grade II	To evaluate tamoxifen for chemoprevention of breast cancer in hysterectomised women.	5408 women aged 35 to 70 years who had hysterectomy for reasons other than neoplasm (low-to-normal risk of breast cancer); no severe concurrent disease, history of cardiac disease, endometriosis or previous DVT; 20% of the participants were on HRT.	Tamoxifen 20mg/day or placebo for 5 years.	The incidence of breast cancer was the primary outcome. Deaths from breast cancer. Adverse events.	Preliminary analysis (low power), median follow-up 46 months (range 0 to 60). No difference in the cumulative incidence of breast cancer between the tamoxifen (19 cases) and placebo (22 cases) groups. A trend towards a beneficial effect of tamoxifen in women on treatment for more than one year. A reduction in breast cancer among women on tamoxifen who also used HRT during the trial did not reach statistical significance (HR 0.13, 95% CI 0.02 to 1.02). Increased risk of vascular events with tamoxifen (P=0.0053), mainly superficial phlebitis; Self-reported hypertriglyceridaemia (correlated with development of atherosclerosis, the underlying cause of heart disease and stroke) with tamoxifen (P=0.0013); 5 confirmed strokes were in the tamoxifen group.	A low power preliminary analysis of a double-blind RCT with adequate concealment of allocation. Drop-out 1422/5408 (26.3%), similar in both groups.



Study, country, grade	Aims of study	Participants	Intervention	Outcome measures	Results	Comments
Veronesi, 1999 <sup>38</sup> Italy Grade II	To evaluate the efficacy of fenretinide to prevent contralateral primaries in women treated for breast cancer.	2867 breast cancer patients (T1-T2) aged 30 to 70 years; no lymph node involvement (N0), local recurrence or distant metastases (M0); no previous post-surgical adjuvant chemotherapy or hormone therapy.	Fenretinide 200mg/day or no treatment for 5 years.	The primary outcome was the occurrence of contralateral breast cancer as the first malignant event, within 7 years of randomisation. A second end-point was the incidence of ipsilateral breast cancer reappearance (local recurrence in the same quadrant, or second malignancy in a different quadrant).  Adverse events were also recorded and graded for severity using modified WHO criteria.	At a median observation time of 97 months (8.1 years) no difference was shown in the occurrence of contralateral (HR 0.92, 95% CI 0.66 to 1.29; P=0.642) or ipsilateral (HR 0.83, 95% CI 0.64 to 1.09; P=0.177) breast cancer. <i>Post hoc</i> adjusted analysis suggested a possible beneficial effect in premenopausal women, and the opposite effect in postmenopausal women.  The most frequent adverse events in women who received fenretinide were diminished dark adaptation (221/1432, 15.4%) and dermatologic disorders (234/1432, 16.3%). 63 women (4.4%) had to stop treatment because of severe adverse events. No difference was shown in liver function tests, lipid profiles, or blood tests between fenretinide and no treatment.	An unblinded multicentre RCT with adequate concealment of allocation. The authors state that the data are exploratory and need to be confirmed.  Loss/exclusions 4.3% in fenretinide group, 2.8% in control group. Power close to nominal level (87%).

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# Patient-Centred Care

## Communication between Health Professionals and Patients

### The Questions

- a. What methods of information giving have been proposed to improve communication with cancer patients, and how effective are they?
- b. What training should senior health professionals be given to improve communication with cancer patients?

### The Nature of the Research Evidence

- a. A systematic review described 10 RCTs of communication strategies used in the diagnostic phase between medical practitioners and patients with various cancers, the aim being to guide clinicians in breaking bad news to cancer patients,<sup>1</sup> (Grade I). A Cochrane review of eight RCTs examined the effects of providing recordings or summaries of consultations to people with cancer and their families,<sup>2</sup> (Grade I). The two reviews had six included RCTs in common. Both reviews are summarised in Table 2a.
- b. A programme to teach senior oncologists to communicate, conducted by the UK Cancer Research Campaign Psychosocial Oncology Group, has published phase I results.<sup>3</sup> This study is summarised in Table 2b. Development of a training workshop on breaking bad news for senior staff in a large district hospital in Plymouth has been described in the literature.<sup>4</sup> An audit of the frequency of poorly broken bad news has been conducted among cancer patients at a hospital in Plymouth (J. Abel, personal communication). Breast cancer services in West Dorset collected consumer audit data in 1993 and again in 1995, including how women were given their diagnosis by a breast surgeon.<sup>5</sup> (Grade VI.)

### Summary of the Research Evidence

- a. A systematic review of RCTs of communication strategies found that the interventions tested were varied and had little effect on psychosocial adjustment and inconsistent effects on patient knowledge levels and satisfaction with care,<sup>1</sup> (Grade I). The implications for practice are not clear due to methodological deficiencies in the trials. Similarly, the Cochrane review, in which there was an overlap of six studies with the Walsh review, reported that there was considerable heterogeneity between the studies in the types of interventions and methods of delivery; in patient populations and cancer sites, in timing of initial intervention and follow-up, and in measured outcomes. The Cochrane review found that between 83% and 96% of participants found recordings or summaries of their consultations valuable (based on 7 RCTs). Four out of six studies

reported better recall of information by those who received recordings or summaries. Two out of four studies found that participants provided with a recording or summary were more satisfied with the information received. None of six studies showed a statistically significant effect on anxiety or depression<sup>2</sup> (Grade D). No study evaluated the effects on survival or quality of life.

- b. That oncologists are hampered by inadequate communication skills has been shown in phase I of a UK study to develop communication skills training courses. Initial results indicate that, with the use of a proven educational approach, practising oncologists can be helped to greater confidence and to adopt changes in their personal and their teaching practices in relation to communication with cancer patients,<sup>3</sup> (Grade VI).

In another UK study, senior doctors, nurses and other professionals allied to medicine demonstrated an overall 20% increase in confidence in dealing with the delivery of bad news to patients and their carers following a short district hospital-based training workshop,<sup>4</sup> (Grade VI). An audit (unpublished) conducted among cancer patients at a Plymouth hospital found that 7/28 patients with a diagnosis of breast cancer said that the news was broken to them in an insensitive manner. The main complaints were: too stern, not enough information, unable to ask questions, no privacy, and failure to mention the word cancer (J. Abel, personal communication). In all, 71 patients with various cancers were interviewed and 15 (21%) of them felt that bad news was broken to them insensitively. Surgeons were the worst offenders, 8/43 (19%) surgeons in the study were said to be insensitive. This suggests that senior health care professionals, including consultants, do need training in breaking bad news (Grade VI).

An earlier short report compared consumer audit data collected in 1993 and again in 1995 in West Dorset. An improvement was shown between the first and second audit in the way women were given their diagnosis of breast cancer, coinciding with the surgeon having attended a communication skills course as recommended by the findings from the first audit,<sup>5</sup> (Grade VI).

**Table 2a. Patient-centred care: systematic reviews**

<b>Study, grade</b>	<b>Aims of study</b>	<b>Included studies</b>	<b>Outcome measures</b>	<b>Results</b>	<b>Comments</b>
Scott, 1999 <sup>2</sup> Grade I	To examine the effects of providing recordings or summaries of their consultations to people with cancer and their families.	8 RCTs that compared the effects of audiotapes or written summaries of consultations with another communication aid or usual care.  Participants (16 to 81 years) had various types of cancer.  Reasons for the consultation included newly diagnosed patients receiving their diagnosis, a first appointment with a medical oncologist or surgeon, and patients with an established diagnosis receiving news that their treatment had been unsuccessful.	Information obtained, recalled and level of understanding; experience of health care; health and wellbeing. Data on participants' use of recordings and summaries, and perceptions of their usefulness were also extracted.	The trials did not all measure similar outcomes.  In seven RCTs, between 83% and 96% of participants found recordings or summaries of their consultations valuable.  Four out of six trials reported better recall of information for those receiving recordings or summaries. Two out of four trials found that participants provided with a recording or summary were more satisfied with the information received.  None of the trials (out of six) found a statistically significant effect on anxiety or depression.  No study evaluated the effects on survival or quality of life.	A good quality Cochrane review.  Six included trials overlap with the Walsh review. <sup>1</sup>  There was considerable heterogeneity between the studies in the types of interventions and methods of delivery, in patient populations and cancer sites, in timing of initial intervention and follow-up, and in measured outcomes.
Walsh, 1998 <sup>1</sup> Grade I	To review the literature on strategies for healthcare providers breaking bad news to cancer patients.	10 RCTs (conducted in Australia, Canada, and the UK, from 1981 to 1996).  1294 cancer patients in the diagnostic phase or the post-diagnostic pre-treatment phase.  Interventions included pre-consultation individualised information, prompt sheet, varying explicitness of clues to diagnosis during consultation, audiotape of consultation, post-consultation handout or summary letter.	Implications for cancer care programmes examined by patient knowledge levels, psychological adjustment, and satisfaction.  One Canadian trial measured the cost of different interventions.	Effects on knowledge levels and information needs were inconsistent across 8 RCTs.  No difference in psychological adjustment was shown in 7/8 RCTs.  Effects on patient satisfaction were inconsistent across 6 RCTs.  Patient rating of the experimental intervention was positive in all 7 RCTs in which they were asked.  The same communication strategies should not be used unvaryingly with all cancer patients.  3 RCTs tended to support the need for providers to assess patients' preferences for information in the consultation in which the bad news is revealed.  In one RCT the cost of a pre-mailed simple information package was less than half that of a more complex package, and was more popular with patients.	Adequate review methodology, possible language bias.  Methodological shortcomings in the RCTs included: sampling procedure, sample size, group comparability, description of control procedures, and use of appropriate psychometric scales. 1 trial was not strictly randomised.

**Table 2b. Patient-centred care: primary study of communication with cancer patients**

Study, country, grade	Aims of study	Participants	Intervention	Outcome measures	Results	Comments
Fallowfield 1998 <sup>5</sup> UK Grade VI	To determine the communication difficulties experienced by clinicians in cancer medicine and to develop, implement, and evaluate communication skills training courses.	178 senior clinicians who attended a 1½ or 3-day course designed to enhance skills development, knowledge acquisition and personal awareness.	Course content included structured feedback, video review of interviews, interactive group demonstrations, and small group discussions led by trained facilitators.	Self-rated confidence in key aspects of communication, attitudinal shift towards more patient-centred interviewing, perceived changes in personal practice, initiation of teaching programmes for junior staff.	<p>Less than 35% of participants has received any previous communication training.</p> <p>Time, experience, and seniority had not improved skills.</p> <p>Pre-course problems concerned giving complex information, obtaining informed consent, handling ethnic and cultural differences.</p> <p>Confidence ratings for key communication areas post-course were significantly improved (P&lt;0.01).</p> <p>3 months post-course, 95% reported significant changes in their practice and 75% had started teaching initiatives in communication for junior clinicians.</p> <p>Clinicians showed positive shifts in attitudes towards patients' psychosocial needs (P=0.0002), and were more patient centred (P=0.03).</p> <p>Resources for educational initiatives are needed to help both patients and their physicians.</p>	Phase I of a study to develop communication skills training courses.

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# Rapid and Accurate Diagnosis

## 1. Diagnostic Services

### The Questions

- a. Is there any evidence relating to patient experience regarding one-stop clinics, in terms of surroundings, location and other aspects of using facilities on one site or at multiple sites?
- b. Should women be informed of their diagnosis on the same day at a one-stop clinic, or is a two-stage procedure better for women?

### Nature of the Research Evidence

- a. A prospective audit of patient acceptance of a one-stop diagnostic clinic at St. Bartholomew's Hospital has been published.<sup>1</sup> (Grade VI, study not tabulated.)
- b. An RCT conducted in Bristol evaluated the psychological impact on 583 women of a one-stop breast clinic compared to a conventional arrangement of two appointments and a delay before diagnosis,<sup>2,3</sup> (Grade II). A cohort study of 126 women investigated psychological distress associated with waiting for diagnostic results in a delayed-results breast clinic in Wales,<sup>4</sup> (Grade VI). An earlier non-randomised study of 102 women who attended symptomatic breast clinics in Leicester compared anxiety levels between those who received their FNAB diagnosis at their initial clinic visit with those who had delayed communication one week later,<sup>5</sup> (Grade V). These studies are summarised in Table 3a.

### Summary of the Research Evidence

- a. A prospective audit (Grade VI) conducted at St. Bartholomew's Hospital over November 1997 reported satisfaction scores for 38 new-attendees who underwent one-stop investigations. Satisfaction was assessed prior to the patients' departure from the clinic using a visual analogue scale from 1 to 10. The mean score was high, 9.24 (range 6 to 10), but no details were recorded about which aspects of the facility contributed to patient satisfaction.<sup>1</sup>
- b. An RCT conducted at a Bristol breast lump clinic assessed women's psychological reactions at their first clinic visit and six days and eight weeks later,<sup>2,3</sup> (Grade II). Women who attended the one-stop clinic waited at the hospital for two to three hours for their diagnosis, women in the two-stop system control group returned for their results one week later. The findings were based on 583 women (out of 791 women who started the study) who completed follow-up (74% of each group). Six days after the first clinic attendance (when only the one-stop group had received their results) case level

anxiety (Hospital Anxiety and Depression Scale) in the one-stop group was significantly lower than in the two-stop group for women with a benign diagnosis (n=518). Among women with breast cancer (n=65), case level anxiety, although higher in the one-stop group, was not significantly different between the one-stop and the two-stop groups at day six. After eight weeks, women with cancer who experienced the one-stop system reported higher levels of depression than women who were given their diagnosis in the two-stop system but on other measures of psychological well-being the two groups were comparable.

A small non-randomised study (Grade V) found women's state of anxiety level to be high before their initial consultation at a symptomatic breast clinic. Of 102 women who had a definitive result following fine needle aspiration biopsy (FNAB), 51 were told their diagnosis at the initial consultation (immediate communication) and 51 were told one-week later (delayed communication). Data were analysed for 97 women who completed all anxiety assessments. In women with benign results (n=81), immediate communication was associated with a significantly greater fall in anxiety from before to after the first consultation. Among 16 of the 17 women who had malignant disease, no difference was shown between immediate and delayed communication.<sup>5</sup>

A small cohort study (Grade VI) explored anxiety, mood and coping in 98 women who attended a delayed results breast clinic (28/126 who entered the study had incomplete data). At the end of their first appointment (having undergone triple assessment) women's anxiety scores (State-Trait Anxiety Inventory) were classified as low, moderate or high. These scores were found not to have changed over the following 3-days while they waited for their results (Profile of Mood States, Daily Coping Scale). No difference was found within or between groups according to whether the eventual diagnosis was malignant or benign. On return to the clinic for their results, women whose anxiety was originally moderate or high showed no significant change, while the low anxiety group showed a significant increase in state anxiety (STAI) immediately before they received their results. Qualitative data (women's own documented thoughts during the waiting period) suggested that women use various coping strategies in the period before they receive their diagnosis, and that the delay may allow time for psychological preparation to receive the test results.<sup>4</sup>

In summary, the RCT and the non-randomised controlled study showed that speedier provision of results to women who do not have cancer can spare them the psychological distress associated with waiting for a diagnosis. On the other hand, neither study showed a difference in psychological effects between same-day and delayed communication of results to women with cancer. The cohort study suggested that a wait of 3 days for test results sustained psychological distress regardless of the final diagnosis. Two studies had a non-random design, one had no control group, loss to follow up was over 20%, and in particular the number of women with a cancer diagnosis was too small for reliable analysis.



## 2. Diagnosis of Primary Disease

### The Questions

- a. Does diagnostic ultrasound of mammography-detected breast lesions assist in the differentiation of benign from malignant disease in newly-presenting breast cancer?
- b. Is MRI more reliable than mammography or US to assess whether disease is multifocal or multicentric (rather than a single tumour)?
- c. Is core biopsy an effective and safe alternative, and is it more acceptable to women, than fine needle aspiration (FNA) in the context of triple assessment diagnosis of primary breast cancer?
- d. Is ultrasound necessary for women with small breast lesions undergoing core biopsy or FNA?

3

### Nature of the Research Evidence

- a. No systematic review was identified. The evidence from primary diagnostic studies is indirect - no study prospectively addressed this question directly but a few have reported some relevant data as part of other investigations. These studies are described below, but not tabulated. (Grade V.)

A study in the UK prospectively classified mammography and ultrasound images to assess the value of these technologies individually and in combination to predict whether a breast abnormality is benign or malignant.<sup>6</sup> Similarly, prospectively recorded final assessment categories for mammography and ultrasound were used in one Norwegian study to assess the additional value of ultrasound to mammography in the diagnosis of breast cancer.<sup>7</sup> A retrospective study compared mammogram and ultrasound classification of breast lesions in a blinded analysis (the two radiologists who reviewed the images were blind to the histological diagnosis).<sup>8</sup>

- b. No systematic review was identified. Three recent primary studies have addressed this question directly and reported sufficient data for review, two were prospective<sup>9, 10</sup> and one retrospective.<sup>11</sup> These studies are summarised in Table 3b. An additional study did not report sufficient data for review.<sup>12</sup>

Several primary studies reported indirect data as part of another investigation, usually tagged on to the end of a sensitivity/specificity comparison of MRI versus mammography/US.<sup>13-18</sup> These studies are not included in this review.

A new Health Technology Assessment (HTA) trial aims to provide information on unifocal cancer defined by mammography and US subsequently shown to be multifocal or multicentric on MRI prior to surgical intervention. This is a multicentre RCT in women with primary breast cancer scheduled for wide local excision following triple assessment (L. Turnbull, personal communication).

- c. No systematic review was identified and a search for experimental studies found none that compared one method as a direct alternative to the other.

There are published data from performance audit surveys (Grade VI) of the use of fine needle aspiration cytology (FNAC) and core biopsy in breast screening centres within the NHS Breast Screening Programme (NHSBSP).<sup>19</sup> Data from a one-year audit of the use FNAC in one UK hospital's one-stop breast clinic have been published as a reminder, the authors say, that good results can be achieved with this method.<sup>20</sup> An earlier study in the US compared sensitivity and specificity of FNA and CB performed concurrently on 124 women,<sup>21</sup> (Grade IV). (Studies not tabulated.)

- d. No systematic review was identified. A search for primary studies identified only retrospective case series of selected patients (Grade VI) who underwent US or stereotactic guided core biopsy,<sup>22-24</sup> or FNAC,<sup>25</sup> or US guided FNAC/B.<sup>26, 27</sup> (Studies not tabulated.)

## Summary of the Research Evidence

- a. Indirect evidence is available from primary diagnostic studies (Grade V).

A UK study prospectively classified mammography and ultrasound findings for 368 women with symptomatic breast disease who had both imaging tests, and correlated imaging categories with histological confirmation based on post-surgical excision (162 benign and 206 malignant).<sup>6</sup> Fifty-eight women had a mammogram classified as 'probably benign' (category 2). In 12/58 the ultrasound finding was 'possibly malignant' or 'probably malignant' (category 3-4); histology was malignant in 5 of the 12. For the other 46/58 women with a 'probably benign' mammogram, ultrasound gave the same result; histology was malignant in 7 of these 46 women.

Of 198 women who had a mammogram classified as 'possibly malignant' or 'probably malignant' (category 3-4), ultrasound gave the same result in 175/198; histology was malignant for 153/175. In the remaining 23/198 the ultrasound finding was downgraded to 'no significant lesion' or 'probably benign' (category 1-2); histology was malignant in 11/23 cases.

One-hundred and twelve women had a normal mammogram ('no significant lesion') where ultrasound indicated a possible or probable malignancy in 42, and histology was malignant in 25 cases.

In this study targeted ultrasound as an adjunct to mammography increased the cancer detection rate by 14%, but at the expense of decreased specificity. The authors emphasised the need for biopsy of any focal lesion identified by mammography or ultrasound. In the presence of a suspicious, mammogram where ultrasound features are also suspicious most of the lesions will be malignant. A suspicious mammogram coupled with a more benign ultrasound reduces the probability of malignancy, but confirmatory pathology is essential. Limitations of the study are that it included a selected population of only women who had undergone surgical excision, and that the radiologist was not blind to the clinical diagnosis while categorising imaging results.<sup>6</sup>

Prospectively recorded final assessment categories for mammography and ultrasound were studied for 327 consecutive malignant tumours confirmed by histology in one study. The additional value of ultrasound was assessed for a subpopulation of 71 of these malignancies after excluding mammography-

conclusive malignant findings, DCIS, and invasive cancers presenting with suspicious calcifications.<sup>7</sup> In the subpopulation, ultrasound correctly upgraded the diagnosis of 20/48 palpable and 10/23 nonpalpable malignant tumours with benign or indeterminate mammographic diagnoses (i.e. a correct upgrading of 43%). The result for only the indeterminate mammograms was 26/58 (i.e. a correct upgrading of 45%). On the other hand, 10/58 malignancies with an indeterminate mammogram were categorised by ultrasound as a 'nonneoplastic abnormality', 7/58 as benign, and 15/58 as an indeterminate tumour.

In one retrospective analysis mammogram and US images of 63 breast lesions (including 39 cancers confirmed by histology) were reviewed by two radiologists blind to the histological diagnosis. Of 13 cancers indeterminate on mammography, ultrasound increased the grade of suspicion of malignancy in 11, and all 11 were confirmed to be malignant by histology (the other two cancers were indeterminate on ultrasound).<sup>8</sup>

Overall, these studies suggest that ultrasound does assist in the differentiation of benign from malignant disease and the combined sensitivity of both tests is better than either alone; but the opposite is true for specificity. The authors stress the need for cytological confirmation (such as needle biopsy, already a standard component of triple assessment) of any focal abnormality detected by either mammography or ultrasound when used in conjunction, to increase the specificity and avoid unnecessary benign surgical biopsies. Ultrasound is commonly used in combination with FNAC or core biopsy and may be unsafe without this tissue diagnosis.

In practice, ultrasound is widely used to assist in the differentiation of benign from malignant disease. Ultrasound machines are getting better and a probe with a minimum frequency of 7.5 MHz is recommended (R. Warren, R. Wilson, personal communication). Machines should not be more than about 5 years old (ca. 1996). Some operators use colour flow Doppler and some use contrast agents, the evidence for which comes from selected cohorts of case material (i.e. weak). Ultrasound is now being undertaken by a variety of operators and is notably operator dependent. Traditionally radiologists undertake the procedure, but latterly surgeons (with or without training) and radiographers are doing so. There is a need for implementation of standards of competence (R. Warren, personal communication). (Grade VII.)

- b. A prospective study (Grade V) investigated the value of pre-operative MRI to detect multifocal or multicentric lesions in 463 women with suspicious lesions indicated by clinical examination, mammography and/or ultrasound. MRI diagnosed multifocal or multicentric disease in 54/92 women, compared to 12 of the 42 multifocal cases and 26 out of the 50 multicentric cases detected by clinical examination, mammography and/or US. The MRI findings changed the treatment management for 51/54 women from lumpectomy to quadrantectomy or mastectomy. MRI gave a false positive finding in 16/463 (3.5%) women who underwent unnecessary open biopsy.<sup>9</sup>

A small prospective study (Grade IV) in 46 women used post-mastectomy histology as the gold standard to determine the sensitivity of MRI to detect multicentric disease. MRI sensitivity was 89% (34/38 cases) compared to 79% (30/38) for the combination of clinical examination, mammography and sonography. MRI had the lowest specificity for multicentric breast cancer, with

8/46 (17%) false positive uptakes of contrast agent by benign tumours. There were 4/38 MRI false negatives, compared to 13/38 false negative mammograms of radiodense breasts in younger women.<sup>10</sup>

An earlier retrospective study (Grade IV) of 60 consecutive women who underwent mastectomy on the basis of clinical findings, mammography or US, reported MRI to be 100% accurate in identifying multifocality (13/13 histology-confirmed cases), compared to mammography (4/13, 31%) and ultrasonography (5/13, 38%).<sup>11</sup>

Overall, these three studies suggest that MRI can increase the detection rate of multifocal or multicentric disease above that achieved by mammography and ultrasound. This information can inform the choice of treatment between lumpectomy and quadrantectomy or mastectomy. There is still room for improvement in the technical application of MRI to improve the specificity of the test (i.e. to reduce the false positive rate). There is also room for improvement in the research methodology. Each of these studies was open to some sources of bias. Of the two prospective studies, both studied a relevant population, although sampling was unclear. Only in the study by Kramer was the gold standard reference test (post-mastectomy histology) applied to all women. Neither study report is clear regarding blinding or independent performance or interpretation of the tests. Both reports do, however, account for all patients not included in analyses. The retrospective study was adequate regarding the population studied, the reference standard used, and the application of tests and reference standard to all participants, however, there was no blinding. The tests were performed independently, but whether interpretation was independent is unclear. Data for all participants were analysed.

The new HTA trial is a randomised multicentre study. It is expected to start recruiting in November 2001. Data will be collected on the rates of re-excision/mastectomy/radiotherapy required as a consequence of positive margins after wide local excision. Rates will be compared between women whose management was planned conventionally by triple assessment (mammography, US and clinical examination) and women whose management was planned by triple assessment and MRI combined. This will provide essential data about the consequences of unifocal cancer as defined by mammography and US, subsequently shown to be multifocal or multicentric on MRI prior to surgical intervention.

- c. A change of practice in many units throughout the UK suggests an increasing acceptance that core biopsy is a more effective pre-operative diagnostic procedure than fine needle aspiration (FNA).

The best evidence to support such a change comes from a performance audit survey of breast screening centres within the NHSBSP,<sup>19</sup> (Grade VI). Data were collated from 85/95 screening centres who returned completed questionnaires on all FNAC and core biopsy procedures performed between April 1996 and March 1997. In total, 13,152 patients had FNAC and 3857 had core biopsy. The audit showed that core biopsy was much more likely to give an unequivocal benign or malignant result - 85% of procedures were categorised as one or the other, compared to 62% for FNAC (although this does need to be interpreted in the light of other performance parameters). There was a much lower rate of inadequate sampling with core biopsy (median 10.6, range 0 to 40; the range

refers to centre performance, worst to best) compared to FNAC (median 23.2, range 4.7 to 75.8). The false negative rate, however, was shown to be higher with CB (median 13.0, range 0 to 100) compared to FNAC (median 6.3, range 0 to 26.7). The authors suggest that with greater experience and closer attention to biopsy technique the CB false negative rate may fall. There was no difference in false positive rates, however, 5/7 false positive core biopsies were shown on review to have been missed at surgery (2/5) or definitely showed malignancy that was not detected by subsequent excision and pathological investigation (3/5). Of the other two, surgical excision showed one radial scar and one atypical ductal hyperplasia. The 13 false positive FNAC cases included atypical ductal hyperplasia, fibroadenoma, and adenomyoepithelioma.

A short report of a one-year (1997) audit of all 601 FNAC specimens from a one-stop breast clinic at the Princess Royal Hospital showed, for FNAC of 138 symptomatic breast cancers, 90.6% absolute sensitivity (calculated from the three definite benign and 125 definite malignant results only) and 97.8% complete sensitivity (also includes 7 'suspicious malignant' and 3 'probably benign' results),<sup>20</sup> (Grade VI). Three FNAC procedures gave false negative results. There were no inadequate samples. Although the authors of both these studies concluded that core biopsy and FNAC, respectively, are well tolerated, they do not appear to have asked their patients.

A small study (Grade IV) in the USA that compared FNA and core biopsy applied concurrently, achieved a specificity of 100% with both techniques when applied to 124 women with a clinically suspicious and palpable breast mass (mean size 4.4cm, range 1 to 12cm). Sensitivity to detect a malignant lesion was 97.5% for FNA compared to 90% for core biopsy ( $P < 0.004$ ). A definite positive diagnosis was made by FNA in 114 cases, plus an additional seven 'suspicious' lesions (the latter were counted as positive in the calculation of sensitivity), a definite positive diagnosis was made by core biopsy in 112 cases. Three false negative FNA results were also negative on core biopsy. The remaining nine false negative core biopsy results were positive (six) or suspicious (three) on FNA. All false negative core biopsies were due to sampling errors which the authors attribute to technical problems in sampling small mobile lesions, decreased tactile sensitivity, and single monodirectional sampling with the core device. Patient preference was not reported.<sup>21</sup>

- d. The use of ultrasound for non-palpable and palpable lesions is to identify whether or not there is a lesion, to assess the probability that it is benign or malignant, and then to guide the biopsy.

Much of the literature on guidance of the biopsy (core biopsy or FNAC) relates to the technical aspects of the procedure and research studies are typically not of high quality. The primary studies identified were reports of retrospective selected case series (Grade VI, studies not tabulated). Ultrasound guidance and stereotactic guidance were both used in some studies according to which method best showed the lesion, and results were not reported separately.<sup>22, 23</sup> In general, the findings indicated that image-guided core biopsy could spare some women further diagnostic (surgical) tissue sampling (79/107 women<sup>22</sup>), and that accuracy can be high (sensitivity 97%, specificity 98.5%<sup>23</sup>). A retrospective study of medical records in one breast centre in the USA showed an increase in the use of image-guided (US and stereotactic) core biopsy, between 1992 and 1996, and a corresponding increase in the malignant yield of open surgical biopsies of

non-palpable lesions. This suggests that image-guided core biopsy eliminates a substantial number of benign abnormalities.<sup>24</sup>

A retrospective review of 137 consecutive patients who underwent US guided FNAC for non-palpable or small palpable lesions at one centre in Japan reported a negative predictive value of 99% (the probability that someone with a negative test does not have the disease).<sup>26</sup> An earlier retrospective analysis of 90 non-palpable lesions in 86 patients in one centre in Finland reported a negative predictive value of 95% for US guided FNAB (positive predictive value 94%).<sup>27</sup> A consecutive series of US guided FNAC of non-palpable lesions in a French institute reported this technique to be reliable for lesions that are not seen only as microcalcifications. Among 92 lesions with benign cytology, 80 were confirmed benign by histology, 12 were malignant (Likelihood Ratio 0.13 i.e. the chance of a benign result among those with disease compared to those without disease). Among 105 lesions with malignant cytology, all were confirmed malignant by histology (21 had suspect cytology, 12 benign and 7 insufficient FNAC samples).<sup>25</sup>

Overall, these studies suggest that image-guided biopsy, including US guidance, of non-palpable lesions or small palpable lesions can reduce the need for more invasive open surgical biopsy. But the research evidence lacks good quality prospective studies.

Modern ultrasound machinery is essential for palpable and non-palpable cancer diagnosis. The group for which ultrasound is not used is those cancers (usually DCIS) which present with calcification. For biopsy of these lesions X-ray stereotaxis is used as the means of localising the correct tissue. Some operators claim to get tissue from calcifications successfully with the very high detail ultrasound machines, but would not do so for every case. This would not be standard practice (R. Warren, personal communication). Stereotactic biopsy should only be used where ultrasound fails to demonstrate the abnormality (R. Wilson, personal communication). Ultrasound guided biopsy is recommended over free-hand technique for both non-palpable and palpable lesions (R. Wilson, personal communication). (Grade VII.)

### 3. Diagnosis of Recurrent Disease

#### The Question

If there is still doubt about the presence of recurrent disease following triple-assessment (including FNAC or CB) does MRI accurately predict the absence of recurrent disease (local recurrence of breast cancer within the breast or chest wall or axilla)?

#### Nature of the Research Evidence

No systematic review was identified. Prospective data from well-designed primary studies of adequate size is lacking.

There are numerous studies of post-treatment MRI that report detection rates of recurrence, but do not address the question of MRI following an equivocal finding from triple assessment, or any single component of triple assessment.

Several more small-sized studies have compared the findings from MRI with those from conventional imaging (mammography and/or US) and/or clinical examination but they do not include cytology or biopsy data (although some do report post-surgical histopathology after re-excision for some patients). Other studies have looked at routine MRI screening for local recurrence. None of these studies are included in this review.

One study prospectively compared triple assessment with MRI, although the reason for performing MRI was not that doubt remained after triple assessment, and only 30 patients were included,<sup>28</sup> (Grade VI).

Four studies were identified that applied MRI to women referred for suspected recurrence, clinical suspicion and/or suspicious conventional imaging, following surgery (some with reconstruction and implants) and radiotherapy. They then compared MRI detection rates of recurrence with an imaging component of triple assessment. They also reported findings from biopsy, although this was apparently performed last to confirm the diagnosis.<sup>29-32</sup> These studies are summarised in Table 3b (Grade IV and V). They are all small and were open to bias from several sources, including selection bias in the populations studied, verification bias, and absence of, or unclear, blinding.

## Summary of the Research Evidence

Mumtaz *et al* examined 30 women prospectively, by triple assessment (clinical examination, mammography and FNAC) and MRI, who had conserving surgery and radiotherapy and a high clinical suspicion of local recurrence within the treated breast.<sup>28</sup> Local recurrence was confirmed by histology in 14 women, seven were identified by mammography, 11 by cytology, and 13 by MRI. Since all clinical examinations were suspicious of recurrence, MRI predicted the presence of malignancy in two cases where there was still doubt following triple assessment (MRI images were examined blind). As there was one false-negative MRI finding the authors stress the need for clinical and cytological evaluation of all patients with suspected recurrence. All 16 true negative results were diagnosed by FNAC. In this small study (Grade IV) the sampling procedure is unclear. All patients had all 4 tests independently and the MRI results were assessed blind. The reference standard was appropriate, and no loss or drop-out is reported.

A French study performed MRI and MRA (angiography) in one examination to investigate 61 cases of suspected recurrence following conservative surgery where conventional imaging (mammography and US) was equivocal. Pathology was confirmed by biopsy (all patients) performed after MRI imaging, or FNA.<sup>31</sup> Pathology showed recurrence in 47/61 women, MRI detected recurrence in all 47 plus 2 false-positives due to inflammation. No false-negative MRI results were reported. The authors describe these results as preliminary (as they also say of later data published only in abstract and insufficient for review<sup>33</sup>). In this study (Grade V) the sampling procedure was unclear, blinding was not reported, nor whether test results were interpreted independently. No loss or drop-out was reported.

A small Italian study used MRI to detect suspected recurrent disease in 12 women, 11 of whom had uncertain mammograms.<sup>29</sup> All 11 had core biopsy and nine also had surgical excision for histology. Among the 11 women with

equivocal mammograms, there was one false-positive and one false-negative MRI (three true-positives, six true-negatives). For both patients who had core biopsy without surgical excision the MRI result was a true-negative (Grade V). The sampling procedure in this study was again not described, blinding was not reported, nor whether test results were interpreted independently. No loss or drop-out was reported. Another very small study used MRI to examine 13 women who had clinically suspected post-lumpectomy recurrence and a questionable mammogram and compared the findings with histology obtained by surgery or core biopsy followed by surgical confirmation.<sup>32</sup> Of eight lesions in seven women with recurrence proved by histology, MRI identified six. There were two false negatives and two false-positive MRI results. The authors advised caution in the use of MRI in the management of suspected recurrent breast cancer because of poor specificity (Grade IV).

No other studies were identified that compared MRI with all three components of triple assessment. The largest primary study identified (n=169, but only 38 patients were symptomatic) compared the detection rate of recurrence achieved by MRI with that achieved by a clinical investigation including mammography (all patients) and/or sonography (144 patients). The women studied had silicone implants following mastectomy.<sup>30</sup> Investigation without MRI detected 8/13 recurrences, whereas adding MRI detected 12/13. MRI also correctly diagnosed scar tissue. The specificity of MRI was low however, due to false positive enhancing granulomas.

The picture that emerges from these studies is that MRI can improve the sensitivity of detection of recurrent disease in surgically treated and reconstructed breasts, over that achieved by conventional imaging mammography and ultrasound. However, the specificity of MRI is not sufficient to obviate the need for cytology or biopsy as well. No studies were found that addressed recurrence of breast cancer in the axilla. Most of the reported data are from very small studies, and all the studies identified were flawed in some way in their methodology. There is a need for adequately sized, well designed and conducted prospective investigations of the role of MRI in this setting.



**Table 3a. Primary studies of one-stop clinics**

Study, country, grade	Aims of study	Participants	Intervention	Outcome measures	Results	Comments
Harcourt, 1999 <sup>2</sup> UK Grade II	To compare the impact on patients of a one-stop clinic versus a conventional arrangement of a minimum of two separate clinic appointments and a delay before test results are provided.	791 women with no previous diagnosis of breast cancer who had a GP referral letter stating the presence of a breast lump, and who lived within travelling distance.  Mean age 43 years (range 16 to 85).	A one-stop clinic where women waited 2 to 3 hours at the clinic for the results of triple assessment, versus a two-stop system where women returned for their results at a separate appointment one week later.	Psychological reactions were measured by questionnaires including visual analogue scales (VAS) to assess worries, concerns and satisfaction with care; the Hospital Anxiety and Depression Scale (HADS) and the European Organisation for the Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) were completed at the first clinic visit and 6 days and 8 weeks later.	Only the 583 women who completed all assessments were analysed (74% of each group).  At the first clinic attendance, prior to diagnosis, 28% of the whole study group reported case levels of anxiety (HADS). There was no significant difference between groups.  Six days after the first clinic attendance only women who attended the one-stop clinic had received their results. Among the 518 women with a benign diagnosis, case level anxiety (HADS) in the one-stop group was significantly lower than in the two-stop group. Among the 65 women with breast cancer, case level anxiety was higher in the one-stop group but was not significantly different from the two-stop group.  Eight weeks after the first clinic attendance, women with cancer who experienced the one-stop clinic (n=38) reported higher levels of depression (HADS subscale) compared to women who experienced the two-stop system (n=27), but on other measures of psychological well-being (HADS, EORTC QLQ-30) they were similar. Women with a benign diagnosis were comparable on all measures at 8 weeks.	A well described RCT with adequate concealment of allocation.  Findings based only on subscale items must be interpreted with caution. The number of women diagnosed with breast cancer was too small for conclusive statistical comparison of one versus two stop clinics.  Total loss to follow-up was 29%; 21 women randomised chose not to participate and 208 did not complete all assessments.
Poole, 1999 <sup>4</sup> UK Grade VI	To investigate the anxiety, mood, and coping behaviours of women waiting for test results in a delayed-results breast clinic.	98 women who attended a delayed results breast clinic and were waiting for the results of biopsies, with no previous psychiatric history.  Mean age 49 years (range 21 to 82).	A peri-diagnostic waiting period between the first clinic visit (including biopsy) and receipt of results at a second clinic visit 3 days later.	Psychological distress was measured by the State-Trait Anxiety Inventory (STAI) before women left the first clinic, and again on the same evening. The Profile of Mood States (POM) and Daily Coping Scale (DCS) were completed on the following 2 days. The State component of the STAI was completed at the results clinic. Women were encouraged to record their thoughts during the waiting period.	Women whose anxiety was moderate or high at their first clinic visit (n=74) showed no significant change on return to the clinic for their results. These women recorded sustained anxiety, depression, uncertainty and confusion. Women whose anxiety was low immediately following the first clinic visit (n=24) retained this state throughout the waiting period, but showed a significant increase in state anxiety (STAI) immediately before they received their results at the second clinic visit.  Women's own documented thoughts during the waiting period showed that various coping strategies are used and suggested that the delay might allow time for psychological preparation to receive test results.	A small non-randomised cohort study without a control group.  Total loss to follow-up was 22%; 28 women had incomplete data (another 6 declined to participate).





<b>Study, country, grade</b>	<b>Aims of study</b>	<b>Participants</b>	<b>Intervention</b>	<b>Outcome measures</b>	<b>Results</b>	<b>Comments</b>
Ubhi, 1996 <sup>5</sup> UK Grade V	To determine if there is a clear advantage for immediate versus delayed communication of biopsy test results, in terms of anxiety, in women who attend a symptomatic breast clinic.	122 women who attended for the first time one of two symptomatic breast clinics, and who had a fine needle aspiration biopsy (FNAB). Age not reported.	Communication of biopsy results immediately or delayed (one week later). Clinic 'A' gave immediate results for the first 6 weeks of the study and clinic 'B' gave delayed results; this was then reversed for the second 6 weeks of the study.	Anxiety and change in anxiety post- and pre-consultation was measured using the State-Trait Anxiety Inventory short form (STAI-SSF) before and after the first consultation. The Hospital Anxiety and Depression Scale (HADS) was completed before the first consultation.	Before the initial clinic consultation 44 women reported anxiety at the case/clinical level, 29 had borderline scores and 49 had normal scores (HADS).  Among women with a benign result, no significant difference was found in anxiety scores between the immediate (n=41) and delayed (n=44) results groups before or after the first consultation. But a significantly greater fall in anxiety (change score) from before to after the first consultation was found within the immediate communication group.  In women with a diagnosis of cancer no differences were shown between the immediate (n=10) and delayed (n=6) communication groups.	A small non-randomised study with a control group. Too small to show reliable differences among women with a diagnosis of cancer.  Data were analysed according to completion of assessments. Loss to follow-up reached 20% for change in anxiety scores.

**Table 3b. Primary studies of MRI to detect recurrent disease**

Study, country, grade	Aims of study	Population	Diagnostic test/ reference standard	Outcome measures	Results	Comments
Fischer, 1999 <sup>9</sup> Germany Grade V	To determine the effect of pre-operative breast MRI in women with suspicious lesions on therapeutic decisions and to define the value of MRI to detect multifocal or multicentric lesions.	463/522 women (out of a total of 6382 who attended a hospital department of radiology in 1 year), who underwent MRI to investigate a breast abnormality indicated by clinical examination, mammography and/or ultrasound. Mean age 54 years (range 21 to 89).	Test: CE-MRI.  Comparator: clinical examination, mammography and/or ultrasound.  Reference Gold standard: histopathology.  Criteria for positive and negative tests are reported.  Multifocal breast cancer defined as two or more foci associated with one ductal network. Multicentric defined as two or more foci in different quadrants.	Sensitivity, specificity, accuracy, positive and negative predictive values for conventional and CE-MRI; change in treatment management consequent to MRI findings.	Histopathology proved 405 malignant lesions in 336/463 women; 92 women had multifocal or multicentric disease.  MRI diagnosed multifocal disease in 30/42 women (42/405 tumours). Pre-operative clinical exam, mammography, US detected 12/42 cases.  MRI detected multicentric disease in 24/50 women (50/405 tumours). Pre-operative clinical exam, mammography, US detected 26/50 cases.  Overall, MRI showed additional multifocal or multicentric disease in 54/463 women which changed treatment management for 51/463 (11%) from lumpectomy to quadrantectomy or mastectomy.  MRI gave false positives in 16/463 (3.5%) women who underwent unnecessary open biopsy (1 case in the ipsilateral breast, 15 cases in the contralateral breast).  Based on a total of 458 lesions (143 benign, 405 malignant) across the entire study, MRI sensitivity was 93%, specificity 65%, PPV 88%, NPV 76%, and accuracy 85%.	Prospective, unblinded study. Sampling unclear. The reference standard was appropriate. All patients did not get the diagnostic test and the reference standard (surgical biopsy). The tests were not performed independently. Reasons were given when data for some patients were not included in the analyses.



Study, country, grade	Aims of study	Population	Diagnostic test/reference standard	Outcome measures	Results	Comments
Kramer, 1998 <sup>10</sup> Germany Grade IV	To assess the efficacy of MRI for the diagnosis of multicentric breast cancer compared to clinical examination, mammography and sonography.	Women (n=46) who underwent modified radical mastectomy for multicentric disease detected by MRI; MRI was performed when preoperative clinical examination, mammography and/or sonography had diagnosed breast lesions and further suspect lesions in the environment of the primary tumour. Age not reported.	Test: CE-MRI Comparators: clinical examination, mammography, sonography. Reference standard: post-mastectomy histology. Criteria for positive and negative tests are reported. Multicentric disease was defined as >4cm distance between the primary invasive tumour and the second invasive focus.	Diagnosis of multicentric breast cancer.	38/46 women had multicentric breast cancer diagnosed by post-mastectomy histology. (Second focal tumours in the other 8 women had benign post-mastectomy histology.) Sensitivity for the diagnosis of multicentric breast cancer: MRI: 34/38 (89%) Clinical examination: 18/38 (47%) Mammography: 25/38 (66%) Sonography: 30/38 (79%) Clinical examination, mammography and sonography: 79%. MRI had the lowest specificity for multicentric breast cancer, with 8/46 false positive uptakes of contrast agent by benign tumours. There were 2, 5 and 7/46 false positives with clinical examination, mammography and sonography, respectively. There were 4/38 false negatives on MRI compared to 13/38 on mammography, the latter caused by radiodense breasts in younger women.	Prospective study, blinding unclear. Sampling unclear. The reference standard was appropriate. All patients had the diagnostic test and the reference standard test. It is unclear whether the tests were performed, or interpreted, independently. All patients were accounted for but not all were included in the analysis of sensitivity.
Boetes, 1995 <sup>11</sup> The Netherlands Grade IV	To evaluate the comparative accuracy of MRI relative to mammography and ultrasonography for assessing the extent (size and multifocality) of breast tumours.	60 consecutive women who underwent mammography on the basis of clinical findings, mastectomy or ultrasonography. Mean age 53 years (range 32 to 72).	Test: CE-MRI Comparators: mammography and ultrasonography. Reference standard: post-surgical histology. Criteria for positive and negative tests are not reported. Multifocal and multicentric disease is not defined.	Size of index tumour and detection of invasive tumour multifocality.	61 tumours were found by histology; 12 contained a multifocal invasive tumour and one contained multicentric lesions at the site of the second invasive tumour. MRI was 100% accurate in identifying multifocality (13/13), compared to mammography (4/13, 31%) and ultrasonography (5/13, 38%). Three additional lesions that fulfilled the MRI criteria for malignancy turned out to be fibroadenomas.	A retrospective, unblinded study in a relevant clinical population. The reference standard was appropriate and all patients had the diagnostic test and the reference standard test. It is not clear whether the results were interpreted independently. All patients were included in the analyses.

Study, country, grade	Aims of study	Population	Diagnostic test/reference standard	Outcome measures	Results	Comments
Mumtaz, 1997 <sup>28</sup> UK Grade IV	To compare breast MRI and triple assessment for the diagnosis of recurrence in patients with high clinical suspicion of local recurrence following conserving surgery.	30 patients with a high clinical suspicion for local recurrence within the treated breast attending for follow-up at one institution. Six patients had a palpable lump and 24 had thickening within the treated breast. All but one had previously had conserving surgery and radiotherapy.  Median interval from surgery to suspected recurrence was 52 months (range 6 to 185).	Test: CE-MRI  Comparator: triple assessment: clinical examination, mammography, FNAC.  Criteria for positive and negative tests are reported.  Histopathological assessment was performed on wide local excision and mastectomy specimens.	Sensitivity and specificity of FNAC, mammography and MRI.	Local recurrence was confirmed by histology in 14 women.  13 cases of recurrence were detected by MRI, 7 by mammography, and 11 by FNAC.  MRI predicted the presence of malignancy in two cases where there was still doubt following triple assessment. There was one false-negative MRI result.  All 16 true negative results were diagnosed by FNAC, whereas MRI gave 2 false positive results.	A small study with unclear sampling. The reference standard was appropriate and all patients had all tests. The tests were performed, and interpreted, independently. MRI images were assessed blind. All patients were included in the analyses.
Buthiau, 1996 <sup>31</sup> France Grade V	To evaluate the diagnosis of relapse using MRI and MR angiography after conserving treatment where mammography and/or US findings were doubtful.	61 patients with suspected recurrence after conserving surgery. (MRI was not used in this study when clinical and mammographic data agreed.)  Median interval from locoregional treatment to suspected recurrence was 6.5 years (range 5 months to 17 years).	Test: MRI and MR angiography in one examination.  Comparator: conventional imaging (including mammography and US).  Criteria for positive and negative tests are reported  Pathology was confirmed by biopsy (all patients) performed after MRI imaging, or FNA.	Diagnosis of relapse and correlation between MRI and pathology.	Recurrence was confirmed by pathology in 47/61 women.  All 47 cases of relapse were detected by MRI. There were 2 false-positives MRI results. No false-negative MRI results were reported.	The authors describe these results as preliminary.  Sampling is unclear. The reference standard was appropriate. Blinding was not reported, nor whether test results were interpreted independently. Tests were performed independently. All patients were included in the analyses.  This study included an additional 19 patients (not reported here) who had MRI to assess their response to neoadjuvant chemotherapy.

Study, country, grade	Aims of study	Population	Diagnostic test/reference standard	Outcome measures	Results	Comments
Sardanelli, 1998 <sup>29</sup> Italy Grade V	To test the diagnostic reliability of CE-MRI to characterise mammographic findings uncertain for recurrent tumour.	11 women who had suspected recurrent tumours after uncertain mammograms. The time interval between initial treatment and suspected recurrence is not reported.	Test: CE-MRI Comparator: mammographic findings and pathology. Criteria for positive and negative tests are reported All 11 women had CB for pathology and nine also had surgical excision for histology (women who had uncertain mammography, negative MRI and negative biopsy did not undergo surgical excision).	MRI true and false positive and negatives.	There was one false positive and one false negative MRI, 3 true positives, and 6 true negatives. The MRI result was a true-negative for both patients who had CB without surgical excision.	A very small data set. Sampling is unclear. The reference standard was appropriate. Blinding was not reported, nor whether test results were interpreted independently. Tests were performed independently. All patients were included in the analyses.  This study included an additional 26 patients (not reported here) who had MRI to assess suspected primary breast cancer.
Heinig, 1997 <sup>30</sup> Germany Grade VI	To evaluate the diagnostic use of contrast enhanced MRI in women with silicone implants following breast cancer.	169 women with silicone implants following breast cancer; 38 were symptomatic (clinical examination, mammography and/or ultrasound), 131 were asymptomatic. Age not reported.	Test: CE-MRI Comparator: mammography (n=169), ultrasound (n=144). Reference standard: histology or follow-up. Criteria for positive MRI were reported.	Detection of recurrence and multicentricity.	8/13 recurrences were detected by conventional imaging whereas 12/13 were detected by MRI. Multicentricity was detected by MRI alone in 2/3 cases. There were 29 false positive lesions on MRI images caused by enhancing granulomas. MRI sensitivity 0.94, negative predictive value 0.99; specificity 0.82, positive predictive value 0.34. Accuracy 0.84 (calculated from 182 lesions detected in 169 women).	A very small data set. Sampling is unclear. The reference standard was appropriate. The study was not blinded. It is unclear whether test results were interpreted independently. Tests were probably performed independently. All patients were included in the analyses.  The impact of MRI on clinical management is not clear.

<b>Study, country, grade</b>	<b>Aims of study</b>	<b>Population</b>	<b>Diagnostic test/ reference standard</b>	<b>Outcome measures</b>	<b>Results</b>	<b>Comments</b>
Cohen, 1996 <sup>32</sup> Canada Grade IV	To determine the sensitivity and specificity of MRI to detect recurrent breast cancer.	13 women with clinically suspected recurrence and a mammogram suggestive of recurrence.  All had undergone lumpectomy 5 months to 8 years previously, and 5 also had post-surgical radiotherapy.  Age 47 to 77 years.	Test: MRI  Comparator: histology and mammographic findings.  Histologic confirmation was obtained in all cases by surgery or core biopsy followed by surgical confirmation.  Criteria for positive and negative tests are reported.	Suspicion of malignancy by MRI classified as low, moderate or high.	Of eight lesions in 7 patients with biopsy-proven recurrence, MRI identified 6. There were 2 false negative and two false-positive MRI results.	Sampling unclear. The reference standard was appropriate. All patients had the test and the reference standard. Two radiologists independently read the MRI images, blind to histology results. The tests were performed, and interpreted, independently. All patients were included in the analyses.  3/16 women entered were excluded because no histology data were obtained.

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# Surgery

## 1. DCIS

### The Question

For which women with DCIS should mastectomy be considered?

### Nature of the Research Evidence

Two systematic reviews have addressed several aspects of the management of DCIS, including for whom mastectomy should be considered (Grade I/III). One is current to April 2001.<sup>1</sup> The other was conducted for the Australian NHMRC and published in 1998, it is being updated as a Cochrane review (not yet available).<sup>2</sup> The more recent review is summarised in Table 4a.

4

### Summary of the Research Evidence

The Canadian review did not find any RCT designed to compare mastectomy with conserving surgery. It did describe an existing meta-analysis of data from five prospective studies (two with control groups), nine retrospective studies (seven with control groups), and 10 clinical series (two with control groups).<sup>3</sup> This gave a summary relative risk of local recurrence at 5 years which was not significantly higher for patients who underwent conserving surgery (with or without radiation) than for those who had mastectomy (RR 2.86, 95% CI 0.77 to 7.56; n=1840 conserving surgery, 567 mastectomy). The result was similar when only patients who had conserving surgery and radiation were analysed (RR 2.16, 95% CI 0.69 to 5.41; n not reported). No significant difference was found in summary relative risks for mortality in the same comparisons. Pooled data for the individual treatments gave a lower estimated 5-year local recurrence rate in women who underwent mastectomy (4.6%, 95% CI 2.3 to 7.6) compared to conserving surgery with or without radiation (21.5%, 95% CI 14.0 to 30.7), but the probability difference was not significant. Conserving surgery plus radiation showed a similar estimated risk of recurrence (10.6%, 95% CI 5.6 to 16.9) to mastectomy (7.3%, 95% CI 2.7 to 14.1). Estimated 5-year mortality was similar for conserving surgery (4.2%, 95% CI 1.4 to 8.5) and mastectomy (3.9%, 95% CI 1.7 to 6.8). These findings need to be interpreted with caution because the analysis involved cross-study comparisons, the included studies were not randomised and some did not have comparison groups; there is also potential for a cohort effect. (Grade III.)

The data from the NSABP B-06 trial of early invasive disease were collected from a subgroup of patients found after randomisation to have non-invasive disease. With an average follow-up of 83 months, the rate of ipsilateral breast cancer recurrence was 43% (9/21) in the lumpectomy only group compared to 0/28 local failures in the mastectomy group. There were two breast cancer deaths in

the lumpectomy group and one in the mastectomy group. Extrapolation from this data subset to DCIS patients in general is limited.

The Australian review described the same RCT (NSABP B-06) and 20 non-randomised studies (n=1344) and concluded that the appropriate use of mastectomy in the management of DCIS is unclear (Grade III). Also, that there were no on-going trials in this area.

In summary, evidence largely from non-randomised studies suggests that conserving surgery can produce similar reductions in local recurrence and mortality as mastectomy.

Consensus based Scottish national guidelines recommend mastectomy for DCIS >4cm, or disease affecting more than one quadrant,<sup>4</sup> but debate exists concerning the lesion size (Grade VII).

## 2. Tumour Excision and Breast Reconstruction

### The Questions

- a. What evidence exists to support the need to excise breast tumours with negative margins, and is there any evidence as to what distance constitutes a clear margin (non-invasive DCIS, as well as invasive cancer)?
- b. What are women's information needs on breast reconstruction surgery?
- c. How do immediate and delayed reconstruction compare in terms of surgical complications, cosmesis and psychosocial outcomes; and do breast surgeons and plastic surgeons get equivalent results?

### The Nature of the Research Evidence

- a. Evidence on patient outcome relative to excision margin comes mainly from retrospective subgroup analysis, and very few data were identified on pathology reporting.

#### **Excision**

A systematic review of surgical management of early breast cancer (stage I and II) touched on the issues of margin excision in terms of recurrence, and the optimal extent of resection in breast conserving surgery,<sup>5</sup> (Grade I). This review is summarised in Table 4a. A retrospective analysis of data from medical records and pathology reports (Grade VI) of women who underwent conservative surgery and radiation therapy for invasive breast cancer at one hospital in the USA examined 10-year outcome according to margin status,<sup>6</sup> Table 4b. The Nottingham City Hospital conducted a prospective audit of recurrence among women who underwent conserving surgery of primary tumours with a prespecified macroscopic surgical margin of clearance (Grade VI).<sup>7</sup>

In the case of DCIS, a systematic review similarly touched on the issues of margin excision in terms of recurrence,<sup>1</sup> (Grade I/III). This review is summarised in Table 4a. A retrospective analysis of recurrence in relation to

margin width in women who underwent conserving surgery for DCIS in a Manchester breast unit has been published (Table 4b).<sup>8</sup>

## Pathology

The Royal College of Pathologists has published a minimum data set for breast cancer histopathology reports with instruction for how excision margins should be recorded.<sup>9</sup> The document is currently being updated.

A UK study has described the frequency with which histopathological features of known prognostic importance are routinely recorded from surgical specimens of invasive breast cancer diagnosed in NHS laboratories in Lancashire and Greater Manchester,<sup>10</sup> (Grade VI, study not tabulated).

An audit of current practice in the UK has begun but is limited to DCIS (I. Ellis, personal communication).

- b. No systematic review was found. Relevant issues have been discussed in a narrative overview,<sup>11</sup> (Grade VII). There is a Department of Health booklet entitled *Breast implants, Information for women considering breast implants*. Information in the booklet was prepared by women who have had breast implants, health professionals, and representatives of interested organisations. Information on implants for patients is also available on the British Association of Plastic Surgeons (BAPS) and Medical Devices Agency (MDA) web sites.
- c. No systematic review was found. Data on surgical complications, cosmesis and psychological and psychosocial issues come mainly from small, retrospective comparisons of selected cohorts. Several different surgical techniques were used in these studies.

## Surgical Complications and Cosmesis

A study in the USA reported the complication rate in a consecutive series of 197 women who underwent immediate or delayed reconstruction with implants between 1987 and 1990.<sup>12</sup> A short report from Germany reported data on problems encountered in 180 immediate reconstruction and 165 secondary reconstruction operations after mastectomy.<sup>13</sup> A retrospective review of perioperative factors and complications in 102 immediate or delayed free TRAM flap breast reconstruction procedures was presented at the BAPS 2000 meeting (abstract only<sup>14</sup>). An Italian study assessed patient-judged cosmetic results of immediate or delayed breast reconstruction using latissimus dorsi myocutaneous flap.<sup>15</sup> (Grade V, studies not tabulated.)

## Psychological and Psychosocial Outcomes

A prospective analysis within the Michigan Breast Reconstruction Outcome Study compared one-year results post-operative psychosocial outcomes in immediate and delayed mastectomy reconstruction cohorts.<sup>16, 17</sup> The psychological impact of immediate rather than delayed breast reconstruction was analysed retrospectively in a UK study.<sup>18</sup> An earlier Spanish study evaluated psychological adjustment in patients who had immediate or delayed reconstruction using implants or TRAM flap.<sup>19</sup> An abstract from the BAPS 2000

meeting reports on a postal survey of patient perspective on primary versus delayed reconstruction (abstract only<sup>20</sup>). (Grade V, studies not tabulated.)

### **Breast Versus Plastic Surgeons**

No research data were found on the results of breast reconstruction achieved by breast surgeons compared to plastic surgeons.

## Summary of the Research Evidence

- a. Excision and pathology are discussed below.

### **Excision: Early Invasive Breast Cancer**

According to a systematic review of surgical management of early invasive breast cancer (stage I and II) there is a suggestion that local recurrence rates may be lower in studies where quadrantectomy was performed compared with studies of lumpectomy, and there is no consensus on the extent of the resection that is necessary in conserving surgery,<sup>5</sup> (Grade D).

A retrospective analysis of clinical outcome according to pathological margin status showed no significant difference in breast relapse-free survival between patients with negative (n=278) and close margins i.e. typically within 2mm of the surgical margin (n=47), or between patients with positive (n=55) and indeterminate (n=491) margins (Grade VI). These were patients treated for invasive breast cancer in the USA between 1970 and 1990. After 10 years follow-up breast relapse-free survival was 98% for patients with negative or close margins compared to 82% for positive or indeterminate margins (P<0.001). Although distant metastasis-free survival and overall survival at 10-years was also better with negative margins, patients with negative margins in this study also had earlier stage disease. Multivariate analysis taking account of tumour stage, node status, and margin status showed that margin status did maintain statistical significance for breast relapse-free survival (i.e. local control), but not for distant metastasis-free survival or overall survival.<sup>6</sup> A prospective audit was conducted by the Nottingham City Hospital, among women with primary tumours less than 3cm who underwent conserving surgery (and radiotherapy) with at least 5mm histological clearance around the tumour, between 1988 and 1992. They found local recurrence in 6/275 (2%) women at a median follow-up of 36 months (Grade VI), a rate as low as any reported at that time.<sup>7</sup>

### **Excision: DCIS**

In the case of DCIS, there is some evidence from the NSABP-B17 trial that positive or indeterminate resection margins increase the risk of local recurrence. Pathology results for 469 women with DCIS who had been treated with breast conserving surgery, with or without postoperative radiation, were analysed retrospectively (Grade V). For women whose margins were less than 1mm there was a significant benefit to radiation therapy in the relative risk of local recurrence, but women whose lesions were excised with margin widths of 1 to <10 mm, or 10 mm or more, did not show increased benefit from radiation.<sup>1</sup> Analysis of data from a Manchester breast unit, collected between 1978 and 1997, showed a higher rate of recurrence among women with close excision

margins ( $\leq 1\text{mm}$ ) compared to women whose margins were clear ( $>1\text{mm}$ ), and that adjuvant therapy may not compensate for inadequate surgical excision of DCIS (Grade VI).<sup>8</sup>

In summary, there is Grade V/VI evidence that incomplete local excision during breast conserving surgery increases the risk of local recurrence in women with primary breast cancer or DCIS. There is as yet no consensus on the actual width of margin needed.

## **Pathology**

There is no consistency or agreement on methods for pathology examination of conservation procedures in the management of breast cancer.

In a study from Greater Manchester and Lancashire, pathology reports for 885 cases of invasive breast cancer (393 assessed in screening laboratories and 492 in non-screening laboratories) were reviewed for details of various histopathological features including the proximity of tumour to the lines of surgical excision. There was substantial interlaboratory variation in the histopathological reporting. Adequacy of excision was recorded in 761 cases (86%), histological type in 843 cases (95%), tumour size in 803 cases (91%), and presence or absence of tumour in vascular channels in 436 cases (49%). Laboratories with low throughput and non-involvement in the breast screening programme were significantly less likely to record certain histopathological features, including the adequacy of lines of surgical excision ( $P=0.024$ ). No significant difference was observed between teaching and non-teaching hospitals,<sup>10</sup> (Grade VI).

- b. The informational needs of women with breast cancer, as discussed in a literature overview (not a systematic review), need to be met at the right time and by several different routes in order to maximise women's chances of being able to make really informed choices. Not all patients want the same amount of information so clinicians need to elicit information preferences for each individual patient,<sup>11</sup> (Grade VII). The Department of Health booklet on implants states that women who consider having breast implants as part of breast reconstruction following mastectomy will find the general principles discussed of value, however, they are also advised to seek specialist advice and information from their surgeon and breast care nurse as the procedures and possible complications are different to those for women who have not had breast cancer.
- c. Research evidence is sparse in this area.

## **Surgical Complications and Cosmesis**

A US retrospective study of breast reconstruction that compared immediate (86 patients/107 breasts) and delayed (57 patients/73 breasts) reconstruction using a permanent implant/expander reported on complications and implant failure. Surgery was performed by one of two surgeons between 1987 and 1990, and follow-up was at least one-year. No difference was found in the rate of minor complications (including infection/skin necrosis, seroma and/or haematoma) or implant failures. Revisional surgery (further surgery that required manipulation of the implant capsule) was significantly higher in the immediate reconstruction group (49 versus 17,  $P=0.001$ ). An anonymous questionnaire about patient

satisfaction yielded a 50% response rate. Ninety percent of immediate reconstruction respondents were satisfied with their reconstruction and all (100%) would do it again, compared to 80% and 90%, respectively, of the delayed reconstruction respondents,<sup>12</sup> (Grade V).

A German article reported problems with infection in 12/180 immediate reconstruction procedures compared to 3/165 delayed operations, the re-operation rate was 15/180 and 8/165, respectively (Grade V). A similar problem rate with the implant/expander was noted, 13 versus 15.<sup>13</sup>

Data from the UK (Dundee) reported six revisions required among 46 immediate TRAM reconstruction operations, of which three were lost, compared to five revisions and one loss among 56 delayed operations. This data is only available in abstract (Grade V). Delayed healing in mastectomy skin flaps only occurred in the immediate reconstruction group (no data); no difference was found in seromas or haematomas; fat necrosis was higher in the delayed group (no data); and adjuvant therapy was delayed for two weeks for two patients who received immediate reconstruction.<sup>14</sup>

A study in Italy reported cosmetic results as judged by patients following latissimus dorsi myocutaneous flap reconstruction. Contralateral surgery was performed in 11/28 (39%) patients who had immediate reconstruction and in 6/15 (40%) who had delayed reconstruction (seven patients who received salvage reconstruction are not reported here). Average follow up was 44 months (range 4 to 270). An excellent or good cosmetic result was reported by 18/28 (64%) immediate and 8/15 (53%) delayed reconstruction recipients (Grade V). One bad result and one failure were reported in the delayed group, none in the immediate group. Complications are not reported in sufficient detail for review.<sup>15</sup>

Overall, these are small studies whose methodology is open to bias. There appears to be a trend towards fewer clinical problems with delayed reconstruction (Grade V). Synthesis is a problem because the studies used different surgical and reconstruction techniques.

### **Psychological and Psychosocial Outcomes**

The main objective of the Michigan Breast Reconstruction Outcome Study was to determine whether the change in psychosocial scores from pre-reconstruction to post-reconstruction varied among three cohorts of women who received tissue expander/implant, pedicle TRAM flap, or free TRAM flap reconstruction (all performed by plastic surgeons). Looking at differences in preoperative and postoperative scores, women who chose immediate reconstruction (n=167) showed significant gains in most psychosocial parameters except social well-being (FACT-B scale) or body image (using a scale designed by the authors) (Grade V). No significant effect on psychosocial scores was noted according to the type of surgical procedure. Among women who chose delayed reconstruction (n=90), no significant gains were shown in social functioning (SF-36 scale) or social well being (FACT-B scale). In the delayed reconstruction group, gains in vitality (SF-36) and social wellbeing (FACT-B) were significantly greater for expander/implant patients, whereas TRAM flap patients showed greater gains in body image (Grade V). This cohort study has limited ability to



control for confounding factors (non-randomised), follow up was only one-year, and complete datasets were not available for all eligible participants.<sup>16, 17</sup>

A retrospective study in the UK aimed to investigate the psychological advantages of immediate rather than delayed breast reconstruction.<sup>18</sup> The mean time since surgery was 61.2 months (range 6 to 226). Of the 38 women who had immediate reconstruction 36 stated that they would still prefer it, and were very or moderately satisfied with the cosmetic result. Of the 83 women who had delayed reconstruction 63 said that they would have preferred immediate reconstruction, and only 61 were very or moderately satisfied with the cosmetic result. No relationship was found between the duration of the delay and patient satisfaction. Obvious impairment of sexual attractiveness was felt by 27 (32%) women who had delayed reconstruction compared to three (8%) women who had immediate reconstruction. Anxiety and depression were less, while body image and self-esteem were better in the immediate reconstruction group than in the delayed reconstruction group (Grade V). An earlier study in Spain also reported impairment regarding body image among women who had delayed reconstruction (48 TRAM flap operations and 20 implants) compared to another group who had immediate reconstruction (2 had TRAM flap operations and 32 implants).<sup>19</sup> A postal survey in the UK that asked a simple question about satisfaction on a linear analogue scale retrieved data from 105 women out of 153 approached which suggested more satisfaction in the delayed reconstruction group ( $P=0.05$ ).<sup>20</sup>

Although the evidence from these studies suggests that women fair better psychologically when their breast reconstruction is immediate rather than delayed, the studies are small, the qualitative data were collected using different tools, and there is considerable potential for bias in the study designs.

### **Breast Versus Plastic Surgeons**

Research evidence on breast reconstruction comparing breast surgeons with plastic surgeons is lacking.

## **3. Management of the Axilla**

### **The Questions**

- a. Does axillary node sampling as an alternative to axillary clearance provide accurate stage determination, result in better informed treatment decisions, reduce recurrence in axillary lymph nodes and improve survival?
- b. What evidence is there to inform whether axillary node dissection should entail removal of all axillary lymph nodes, removal of level I and II nodes, or axillary sampling in invasive breast cancer?
- c. Is axillary node sampling plus radiotherapy better than axillary clearance without radiotherapy in terms of local recurrence and quality of life?

## The Nature of the Research Evidence

- a. The only study that has been identified is the Edinburgh trial (an RCT) in which level III axillary node clearance was compared with axillary node sample in women with operable invasive breast cancer,<sup>21, 22</sup> (Grade II).
- b. No systematic review was identified. One RCT and two retrospective cohort studies have been described in an up-to-date summary in *Clinical Evidence*,<sup>23</sup> (Grade II and V) and no additional studies were identified.
- c. No systematic review was identified. Some data were generated from the Edinburgh trial.<sup>21</sup> No audit data, published or unpublished were retrieved.

## Summary of the Research Evidence

- a. Published data from the Edinburgh trial at a median follow-up of 4.1 years showed no statistically significant difference between level III axillary node clearance and axillary node sampling in overall or disease-free survival, or in the time to axillary or breast cancer recurrence,<sup>21</sup> (Grade II). Updated data, presented in abstract only, suggest a slightly better outcome in terms of local recurrence with axillary clearance<sup>24</sup> (R. Mansel, personal communication).
- b. One RCT (n=417) published in 1985, of node sampling versus axillary clearance, and two large retrospective cohort studies published in 1992 (n=13,851, and 1446) have been described in *Clinical Evidence*.<sup>23</sup> The RCT found that sampling (which aims to remove the four largest palpable nodes) provided sufficient information for accurate staging of the axilla, the cohort studies suggested that accurate staging could be achieved by level I dissection if at least 10 nodes were removed (Grade II and V). Stronger data may emerge from on-going RCTs that compare sentinel node biopsy with axillary sampling and clearance.
- c. The Edinburgh trial made a randomised comparison of axillary clearance versus sampling. Radiotherapy following axillary sampling was selective, not randomised. Data on recurrence were reported only for the randomised comparison of clearance versus sampling, and 39% of women in the sampling group had radiotherapy to the axilla (91/234, intention-to-treat analysis). No difference was shown in local, distant or axillary recurrence,<sup>21</sup> (Grade II). Quality of life was not reported but the trial investigated arm and shoulder morbidity in 234 women who completed the assessment, and who were analysed according to the treatment they received. Eighty-seven women underwent sampling without radiotherapy to the axilla, 74 underwent sampling with radiotherapy, and 163 underwent axillary clearance without radiotherapy. Morbidity was least in those women who had node sampling without radiotherapy to the axilla,<sup>21</sup> (Grade V).

## 4. Sentinel Nodes

### The Questions

- a. Does sentinel lymph node biopsy provide accurate staging of the axilla in patients with breast cancer?

- b. Does sentinel lymph node biopsy avoid the morbidity associated with more extensive axillary dissection?

## The Nature of the Research Evidence

- a. There is a meta-analysis (Grade III) of published patient series of sentinel lymph node biopsy which reports on how often the sentinel lymph node was negative for cancer when malignancy was found in the axillary lymph node dissection.<sup>25</sup> An additional primary study published in the same year was also identified.<sup>26</sup> These studies are summarised in Tables 4a and 4b, respectively.

The ability of sentinel node biopsy to predict axillary status has been examined by Veronesi *et al* in women who specifically requested sentinel node biopsy instead of routine axillary dissection outside of research protocols. These women (with breast cancer and clinically negative axillary nodes) underwent breast surgery and sentinel node biopsy. Where the sentinel node was negative, no dissection was performed and these patients were followed up with clinical examination to monitor the occurrence of axillary node metastasis.<sup>27</sup> (Grade VI, Table 4b.)

A prospective observational study in the USA aimed to determine the rates of complications and recurrence in women who underwent sentinel node biopsy as the sole axillary procedure in the absence of sentinel node metastases.<sup>28</sup> (Grade VI, Table 4b.)

Audit phase data have been collected from a planned two-phase multicentre trial, Axillary Lymphatic Mapping Against Nodal Axillary Clearance (ALMANAC).<sup>29</sup>

The NSABP B-32 trial is an on-going RCT comparing sentinel node resection with sentinel node resection followed by conventional axillary node dissection in women with clinically node negative breast cancer. The trial aims to recruit 2000 patients in to each group and will examine the sensitivity of the sentinel node to determine the presence of nodal metastases. The technical success rate of sentinel node resection, and variability among a broad population of surgeons will also be assessed. Other outcomes include control of regional disease, disease-free survival and overall survival. The ACSOG Z0010 prospective trial is evaluating the significance of sentinel node and bone marrow micrometastases in women whose sentinel nodes are negative when processed by haematoxylin and eosin staining. The trial randomises women with tumour positive sentinel nodes to receive axillary lymph node dissection or no axillary lymph node dissection.

- b. No systematic review or primary study data for morbidity were found. The on-going NSABP B-32 trial of sentinel node dissection with or without conventional axillary node dissection will examine the morbidity associated with these procedures. The ongoing ACSOG Z0011 trial in the USA has randomised women who have undergone sentinel lymph node dissection, to axillary lymph node dissection followed by breast radiotherapy or breast radiotherapy only. The study will quantify and compare surgical morbidity associated with sentinel lymph node dissection with or without axillary node dissection. The study aims to recruit 1900 patients over 3.8 years.

## Summary of the Research Evidence

- 4
- a. A meta-analysis included 11 published series of patients (n = 912) with breast cancer who had sentinel lymph node biopsy followed by standard axillary lymph node dissection.<sup>25</sup> The studies included patients with clinically positive or negative axilla (Table 4a). Overall the sentinel node was identified in 762 patients (83.6%) and its histology was the same as the axillary lymph dissection in 747 cases (98%) (Grade III). In 15 cases where the axillary dissection was positive for malignancy, the sentinel node was negative, giving a false negative rate of 5.1% (15/296). There was no statistical difference in concordance rate or false negative rate shown by subgroup analysis of sentinel node biopsy using dye or radiocolloid, or both, or whether injection was around the intact tumour or the biopsy cavity, or according to invasive or in situ cancer, or clinically positive or negative axilla. Three studies (n=274) reported the axillary node dissection findings where the sentinel node was not identified, 17/53 (32%) of such cases had malignancy in the axilla. Of the 281 malignant cases in which the sentinel node was identified, the sentinel node was the only node positive for malignancy in 146 cases (52%). The included studies are largely from surgeons experienced in sentinel node biopsy (no details given) and the authors suggest that surgeons should demonstrate a false negative rate no greater than 5% before they consider using sentinel node biopsy over axillary dissection,<sup>25</sup> (Grade III). The findings from an additional primary study are in line with those shown in the meta-analysis: the sentinel node was located in 64/79 (81%) patients, and its histology was the same as the axillary lymph node dissection in 63 cases (98.4%), and there was one false negative sentinel node biopsy where the axillary dissection showed malignancy.<sup>26</sup>

In the Italian study of women who chose sentinel node biopsy instead of routine axillary dissection, 379 sentinel node biopsies were performed (6/373 women had bilateral carcinoma).<sup>27</sup> The sentinel node was negative in 285 biopsies, no dissection was performed and the 280 women concerned were followed-up quarterly with clinical examination of the axilla. At the time when a total of 343 years-at-risk were available for evaluation, no cases of clinically evident axillary node metastasis had occurred out of an expected seven. One woman developed a local breast recurrence and one developed distant metastatic bone disease. Ninety-four axillary dissections were performed because the sentinel node was positive, in 63 cases the sentinel node was the only positive node. From this series the authors concluded that sentinel biopsy should be the procedure of choice for staging axillary nodes in women with small-sized breast cancer and clinically negative nodes (Grade VI).

An observational study in the USA (Grade VI) reported data on a consecutive series of women with clinically negative nodes. Sixty-seven women were found to have negative sentinel nodes and, therefore, sentinel lymph node dissection was the only axillary procedure performed. Fifty-seven women who were found to have positive sentinel nodes went on to have axillary lymph node dissection (31 immediately and 26 in a second procedure). One woman in whom the lymph node mapping procedure was unsuccessful also underwent axillary node dissection.<sup>28</sup> At a median follow-up of 39 months there were no local or axillary recurrences. Complications occurred in 20/58 women who underwent axillary lymph node dissection (including seroma, wound infection, haematoma and chronic lymphoedema), and in 2/67 (superficial cellulitis and seroma) who had only sentinel lymph node dissection (P=0.001).

The ALMANAC study audit phase has shown that trained British surgeons can perform the sentinel node biopsy procedure with a success rate greater than 95% and a false negative rate of around 5% (R. Mansel, personal communication). (Grade VI, data not yet published.)

It is anticipated that ongoing large multicentre studies will provide a definitive answer as to whether sentinel lymph node dissection can replace axillary lymph node dissection. Findings are awaited from the ongoing NSABP B-32 and ACSOG Z0010 trials.

- b. Findings are awaited from the on-going NSABP B-32 and the ACSOG Z0011 trials.



**Table 4a. Surgery: systematic reviews**

Study, grade	Aims of Study	Included studies	Outcome measures	Results	Comments
Mirsky 2001 <sup>5</sup> Grade I	To address the questions: What is the optimal surgical management for early stage I and II invasive breast cancer? What is the relative efficacy and safety of breast conservation therapy (lumpectomy plus axillary dissection) compared with modified radical mastectomy?	7 RCTs of conservation therapy versus modified radical mastectomy. 2 RCTs of axillary dissection.	Survival, local recurrence (for lumpectomy patients), quality of life.	<i>Conservation therapy versus mastectomy:</i> Results from 7 RCTs (n= 5089) showed that 5 to 10-year survival was similar following mastectomy compared to lumpectomy plus radiation. Rates of local recurrence varied widely between the trials (0.28% to 26%; 2.4 to 18% in trials where axillary dissection was done with lumpectomy). <i>Axillary dissection:</i> In one RCT (n=658), 3 axillary recurrences occurred in the group who had lumpectomy with axillary node dissection plus breast radiation compared to 7 among those who received lumpectomy plus breast and axillary radiation (RR 3.0, P=0.05). Some women with positive nodes received adjuvant chemotherapy which might account for the survival advantage shown in the axillary dissection group. In the second RCT the risk of axillary recurrence was significantly increased with mastectomy alone (17.8%) compared to radical mastectomy (1.4%) or mastectomy plus radiation (3.1%), among women with clinically negative nodes. Among women with clinically positive nodes, the risk of local recurrence was lower with radical mastectomy (1.0%) versus mastectomy plus radiation (11.9%). This trial showed no 10-year survival advantage with axillary dissection. <i>Quality of Life:</i> The trials reported insufficient information on quality of life to reach a definitive conclusion.	A thorough review that is updated regularly. New evidence is currently being reviewed by the authors.
Wright 2001 <sup>1</sup> Grade I/III	To address the questions: What is the optimal surgical management of DCIS? Should breast irradiation be offered following breast conserving surgery or lumpectomy? Are there patients who can be spared irradiation post lumpectomy? What is the role of tamoxifen?	Surgical management: 1 meta-analysis of 5 prospective and 9 retrospective studies and 10 clinical series (13/24 studies had no control group) <sup>3</sup> . Radiation following breast conserving surgery: Meta-analysis of 2 RCTs (8-year results from NSABP B-17, and 4-year results from EORTC 10853). Omission of radiation following breast conserving surgery: cohort studies and prospective series.	Overall survival, disease-free survival, local recurrence, distant recurrence, quality of life.	<i>Surgical management:</i> meta-analysis of cohort studies and clinical series showed a higher, but not statistically significant, relative risk of local recurrence at 5 years in patients who had conserving surgery (with or without radiation) compared to those who had mastectomy (RR 2.86, 95% CI 0.77 to 7.56; n=1840 conserving surgery, 567 mastectomy). The result was similar when only conserving surgery plus radiation was compared with mastectomy (RR 2.16, 95% CI 0.69 to 5.41). No significant difference was found in the relative risk of mortality. Pooled analysis of treatments individually showed a lower estimated 5-year local recurrence rate in women who underwent mastectomy (4.6%, 95% CI 2.3 to 7.6) compared to conserving surgery with or without radiation (21.5%, 95% CI 14.0 to 30.7), but the probability difference was not significant. Conserving surgery plus radiation showed a similar estimated risk of local recurrence (10.6%, 95% CI 5.6 to 16.9) to mastectomy (7.3%, 95% CI 2.7 to 14.1). Estimated 5-year mortality was similar for conserving surgery (4.2%, 95% CI 1.4 to 8.5) and mastectomy (3.9%, 95% CI 1.7 to 6.8). Tests for homogeneity were not statistically significant, however, interpretation of the findings is very much limited by the design of the primary studies and cross-study comparisons in the meta-analysis. <i>Breast irradiation following conserving surgery:</i> Meta-analysis of 2 RCTs (n=1824) gave a relative risk (RR) of 0.53 (95% CI 0.42 to 0.66, P=0.00001) in favour of conserving surgery plus radiotherapy versus no radiotherapy for local recurrence. The RR for contralateral recurrence favoured patients who did not receive radiotherapy (1.88, 95% CI 1.12 to 3.16, P=0.017)	A thorough review that is updated regularly. The findings from the meta-analysis <sup>3</sup> need to be interpreted with caution as it involved cross-study comparisons, non-randomised studies, and studies without comparison groups.

Study, grade	Aims of Study	Included studies	Outcome measures	Results	Comments
		Tamoxifen: 1 RCT of lumpectomy, radiation and tamoxifen versus lumpectomy, radiation and placebo (NSABP B-24).		<p><i>Omission of radiation following conserving surgery:</i> Cohorts and patient series suggest that the risk of recurrence may be identified by tumour size, margin width and pathological classification, and that low risk women may not benefit from adjuvant radiation. Interpretation is limited by the non-randomised historical comparisons and small patient sub-groups.</p> <p><i>Tamoxifen:</i> an RCT (n=1084) of tamoxifen versus placebo, following lumpectomy and radiation, showed fewer breast cancer events at 5-years with tamoxifen (8.2 versus 13.4%, P=0.0009). A lower incidence rate in invasive recurrence (4.1% versus 7.2%, P=0.004), and a trend towards significance in non-invasive recurrence (4.2% versus 6.2%, P=0.08).</p>	
Miltenburg, 1999 <sup>25</sup> Grade III	To perform a meta-analysis of all published studies of sentinel node biopsy in breast cancer, to identify the rates of identification, concordance with axillary dissection, and false negatives.	<p>11 published series of breast cancer patients (n=912) who underwent sentinel lymph node biopsy followed by standard axillary lymph node dissection.</p> <p>Pathological analysis in all studies used haematoxylin and eosin staining.</p> <p>6 studies were in invasive disease, 3 in invasive and in situ disease, and in 2 studies this was not specified.</p> <p>5 studies were in only clinically negative axilla, 3 in positive or negative, and in 3 studies this was not specified.</p>	Sentinel node identification rate, rate of concordance between the sentinel node and axillary dissection, rate of false negative sentinel nodes.	<p>The sentinel node was identified in 762 patients (83.6%). The sentinel node was the only positive node in 146 of these biopsies (19%).</p> <p>The histology concordance rate was 98% (747/762) between the sentinel node and axillary dissection.</p> <p>The false negative rate was 5.1% (15 negative sentinel nodes out of 296 malignant axillary dissections).</p> <p>Subgroup analysis showed that the sentinel node identification rate was higher (95.3% versus 71.5%) in studies of only patients with invasive cancer (n=449) compared to studies in patients with invasive or in situ cancer (n=438). Similarly (95.9% versus 76.6%), for studies in patients with clinically negative axilla (n=342) compared to studies in patients with or without clinical lymphadenopathy (n=303). The concordance rate and false negative rate were not significantly different among these groups.</p> <p>The concordance rate and false negative rate were not significantly different with respect to the technique of sentinel node biopsy (dye or radiocolloid), nor whether injection was around the intact tumour or the biopsy cavity.</p> <p>Three studies (n=274) reported the status of the axillary nodes in 53 patients in whom the sentinel node could not be identified, in 17 cases (32%) axillary node dissection revealed metastatic malignancy.</p> <p>One complication was reported in 346 successful sentinel node biopsies, due to systemic absorption of blue dye causing a transient fall in oxygen saturation.</p>	Sources searched are not reported, however, a search for primary data identified only 1 additional study that was published in the same year as this review. <sup>26</sup> The conclusions are balanced and do not rest only on the subgroup analyses.





**Table 4b. Surgery: primary studies**

Study, country, grade	Aims of study	Participants	Intervention	Outcome measures	Results	Comments
Chan 2001 <sup>8</sup> UK Grade VI	To determine the excision margin width required in breast conserving surgery for DCIS.	205 women who underwent breast conserving surgery for DCIS of 4cm or less, in a Manchester breast unit between 1978 and 1997, for whom margin width could be reviewed and who had a minimum follow-up of one year. Mean age 56 years (range 19 to 82).  31 women with microinvasive DCIS and 8 without a record of margin width were excluded.	Wide local excision with the goal of obtaining clear margins and cavity shavings. 129 women had no adjuvant therapy, 49 had tamoxifen, 18 had radiotherapy, 9 had tamoxifen and radiotherapy.  Median follow-up was 47 months (range 12 to 197).	Recurrence.	Analysis by margin status was grouped as close ( $\leq 1$ mm) or clear ( $> 1$ mm). Clear margins were subgrouped as 1.1 to 5mm, 10.1 to 40mm, and 10.1 to 40mm.  Recurrence affected more women (25/66, 37.9%) with close margins than women with clear margins ( $P < 0.001$ ); 4/89 (4.5%) with clear margins 1.1 to 5mm, 2/28 (7.1%) with margins 5.1 to 10mm, and 1/22 (4.5%) with margins 10.1 to 40mm had recurrence.  Of the women who had no adjuvant therapy, 4/86 (8.1%) with clear margins had recurrence compared to 14/43 (39.5%) with close margins ( $P < 0.001$ ). Close margins ( $P < 0.001$ ) and nuclear grade 3 ( $P = 0.03$ ) were predictors of recurrence (univariate analysis) following excision alone.  Adjuvant therapy was not shown to compensate for inadequate surgical excision, although patient numbers in the adjuvant treatment groups were low.	An observational study with no controls. Data collection was retrospective up to 1993 and prospective thereafter. From 1992 some patients entered the UK DCIS trial of adjuvant radiotherapy/tamoxifen.
Chetty 2000 <sup>21</sup> UK Grade II	To compare the efficacy of axillary node sample versus axillary clearance in patients with operable breast cancer being treated by breast conservation.  Also to assess the morbidity associated with these procedures and radiotherapy.	466 women with unilateral invasive breast cancer (4cm or less) with no evidence of metastatic disease. Median age 54 years.  Excluded were clinically multicentric tumour, locally inoperable tumour (T4), or fixed nodes (N2).	Axillary node sample versus level III axillary clearance.  Sampling aimed to obtain at least 4 palpable nodes.  Radiotherapy to the axilla was given selectively.	Local, axillary and distant recurrence and survival. Morbidity to the shoulder and arm.	Median follow-up was 4.1 years.  No difference was shown in local, axillary or distant recurrence, or in overall survival, or disease-free survival. There was no difference in time to axillary recurrence or time to breast recurrence.  324 women completed morbidity assessments and were analysed by treatment received (87 underwent sampling without radiotherapy to the axilla, 74 underwent sampling with radiotherapy to the axilla, and 163 underwent axillary clearance without radiotherapy). Axillary clearance was associated with a significant increase in arm volume of 4% that remained constant over the next 2.5 years. At 6 months women who had axillary clearance, or sampling and radiotherapy, had a significantly reduced range of shoulder movement compared to women who had axillary sampling without radiotherapy. However, by 3 years the clearance group improved to a level that was not significantly different from women who had sampling alone.	An unblinded RCT with adequate concealment of allocation. Women were recruited between 1987 and 1995.



Study, country, grade	Aims of study	Participants	Intervention	Outcome measures	Results	Comments
Giuliano, 2000 <sup>28</sup> USA Grade VI	To determine the recurrence and complication rates in patients undergoing sentinel lymph node dissection as the sole axillary procedure in the absence of sentinel node metastases.	125 out of 133 consecutive women with invasive breast cancer and clinically negative nodes. Mean age 58 years (range 32 to 89). Exclusion criteria were lesions >4cm, multifocal tumours, locally advanced disease, disease diagnosed by large excisional biopsies or formal resection.	Sentinel lymph node dissection. Lymphatic mapping and sentinel lymph node dissection was performed using vital blue dye.	Recurrence and complication rates. Complications included seroma, wound infection, haematoma, cellulitis and chronic lymphoedema.	Sentinel nodes were identified in 132/133 patients. 57/125 patients evaluated had positive sentinel nodes and underwent axillary lymph node dissection (31 immediately and 26 in a second procedure), 1 patient who had an unsuccessful mapping procedure also underwent axillary lymph node dissection. sentinel lymph node dissection was the only axillary procedure in the remaining 67 patients. At a median follow-up of 39 months there were no local or axillary recurrences. Complications occurred in 20/58 patients who underwent ALND, and in 2/67 who underwent SLND only (P=0.001).	A prospective observational study conducted from October 1995 to July 1997. Eight women were excluded from the analysis, reasons given.
Jaderborg, 1999 <sup>26</sup> USA Grade VI	To compare histological findings from sentinel lymph node biopsy with concurrent axillary lymph node dissection.	79 women with invasive breast cancer undergoing surgery at two teaching hospitals. Mean age 59 years (range 32 to 84 ).	Sentinel lymph node biopsy followed by axillary dissection including levels I, II and occasionally III. Radiocolloid and vital blue dye, injected around the tumour, were used to locate sentinel nodes.	Sensitivity, specificity, PPV, NPV and accuracy of sentinel node biopsy.	The sentinel node was located in 64/79 (81%) patients. The sentinel node histology was the same as the axillary dissection in 63/64 cases (98.4%); benign in 44 cases, malignant in 19 cases. There was 1 false negative (i.e. benign sentinel node, positive axillary dissection). The sentinel node was the only positive node in 14/64 patients (21.9%). Based on 64 patients in whom the sentinel node was located, sensitivity was 95%, specificity 100%, PPV 100%, NPV 97.8%, and accuracy 98.4%.	A prospective study. Sampling unclear. The reference standard was appropriate. The tests were performed, and interpreted, independently. SN and ALND specimens were examined by different pathologists. 12 recruited patients were excluded from the analysis, reasons given.





Study, country, grade	Aims of study	Participants	Intervention	Outcome measures	Results	Comments
Obedian, 2000 <sup>6</sup> USA Grade VI	To determine the impact of final pathologic margin status on breast relapse-free survival, and overall survival in patients who undergo conservative surgery and radiation therapy for invasive breast cancer.	871 women who underwent conservative surgery and radiation therapy for invasive breast cancer at one US hospital from 1970 to 1990, and for whom pathology reports were available for review. Median age 57 years (range 20 to 86).  Margin status was defined as the margin after wide excision biopsy or re-excision biopsy (n=294).	Routine wide local excision with or without axillary dissection followed by external beam radiotherapy.  Median follow-up was 13 years (range 7 to 27).	Breast relapse-free survival, distant metastasis-free survival, overall survival.	Analysis by margin status was grouped as negative (n=278), close i.e. typically within 2mm of the surgical margin (n=47), positive (n=55), or indeterminate (n=491).  There was no significant difference in breast relapse-free survival between patients with negative and close margins, or between patients with positive and indeterminate margins (data not given). At 10-years, breast relapse-free survival was 98% for patients with negative or close margins compared to 82% for positive or indeterminate margins (P<0.001).  At 10-years, distant metastasis-free survival was 91% for negative margins, 77% for close margins, 72% for positive margins and 77% for indeterminate margins. Overall survival was 85% for negative margins, 72% for close margins, 67% for positive margins and 74% for indeterminate margins. However, patients with negative margins were the most likely to have T1 tumours, mammogram detected lesions, and to be N0.  Patients with negative margins also had earlier stage disease. Multivariate analysis taking account of tumour stage, node status, and margin status showed that margins status did maintain statistical significance for breast relapse-free survival (i.e. local control), but not for distant metastasis free survival or overall survival.	An observational study with no controls. Retrospective statistical analysis of data from medical records.  The high number of indeterminate margins reflects the era in which most patients were treated, when surgeons did not routinely mark biopsy specimens and pathologists did not routinely comment on margin status.
Veronesi, 2001 <sup>27</sup> Italy Grade VI	To evaluate sentinel node biopsy outcome and risks in patients who specifically requested the procedure, outside of research protocols, instead of routine axillary dissection.	373 women with breast cancer and clinically negative axillary nodes who chose sentinel node biopsy instead of routine axillary dissection, outside of research protocols.  40.8% were aged ≤50 years, 32.2% were over 60 years.	Sentinel node biopsy.  Radiolabelled albumin particles injected around the tumour was used to locate sentinel nodes.  Women who had negative sentinel nodes received quarterly follow-up with clinical examination of the axilla.	Data on axillary staging were recorded and the occurrence of clinically evident axillary node metastases was monitored.  A total of 343 years-at-risk were available for analysis.	379 sentinel node biopsies were performed (6/373 women had bilateral carcinoma and bilateral biopsy).  The sentinel node was negative in 285 biopsies and no further dissection was performed (280 women). No cases of clinically evident axillary node metastasis had occurred, out of an expected seven, when a total of 343 years-at-risk were available for evaluation. One woman developed a local breast recurrence and one developed distant metastatic bone disease.  Among 94 axillary dissections that were performed because the sentinel node was positive, the sentinel node was the only positive node in 63 cases. (The sentinel node could not be identified in an additional 4 patients who were excluded from the analysis.)	An observational study with no control group. Conducted from March 1996 to December 1999. Participants were told that SNB was not standard treatment, and that RCTs were ongoing. Follow-up is continuing.

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# Radiotherapy

## 1. Radiotherapy Services

### The Question

Has good radiotherapy practice in the delivery of locoregional treatment been defined in national guidelines, if so is this based on expert opinion or research/audit evidence?

### The Nature of the Research Evidence

Good radiotherapy practice in the delivery of locoregional treatment has not been defined in national guidelines for England and Wales (RCR, personal communication). Detailed guidelines for the technical aspects of therapeutic radiation treatment have been published by the NHMRC National Breast Cancer Centre, Sydney, Australia, but to what extent these are evidence or consensus based is unclear.<sup>1</sup> The Royal College of Radiologists (UK) point to the *Good Practice Guide for Clinical Oncologists, Guidelines for External Beam Radiotherapy*<sup>2</sup> and *Guidelines on the Non-Surgical Management of Breast Cancer*,<sup>3</sup> both produced by the Clinical Oncology Information Network (COIN). These guidelines are expert consensus (Grade VII), although COIN does draw upon existing systematic reviews including those conducted by the Early Breast Cancer Trialists' Collaborative Group and the NHS Executive Cancer Guidance. In addition, there is a SIGN Guideline on when adjuvant radiotherapy should be given.<sup>4</sup>

Technical aspects of radiotherapy planning are being changed by advances in computerised 3D planning with virtual treatment simulation based on 3D X-ray computer tomographic images, e.g. Goodman *et al.*<sup>5</sup> The accuracy of treatment delivery is being changed by the ability of modern treatment machines (linear accelerators) to modulate field shape and beam intensity during therapy under computer control and to verify this in real time using digital imaging and dose monitoring, e.g. Evans *et al.*<sup>6</sup> An RCT in 300 women with early breast cancer at the Royal Marsden Hospital has tested individualised 3D radiotherapy treatment planning with standard 2D tissue compensators in terms of patient self-assessments of treatment morbidity, and results are awaited (J. Yarnold, personal communication).

The on-going START RCT has standardised radiotherapy practice in the delivery of local regional treatment following local excision or mastectomy in women with early stage breast cancer in the 35 participating radiotherapy departments in the UK (about 70% of the total). The definitions of target volume, patient position, field arrangements, beam quality, dosimetry, treatment delivery, verification, dose prescription and scheduling with other treatments are all prescribed in the protocol.<sup>7,8</sup> The START trial is primarily testing alternative radiotherapy dose fractionation schedules, an area of uncertainty in clinical practice that has also been addressed by one RCT in the UK (West Midlands

Breast Group) and one Canadian RCT,<sup>9</sup> from which full publication of results is awaited.

## Summary of the Research Evidence

Evidence relating to technical advances in radiotherapy planning and delivery is accumulating rapidly with respect to improved treatment accuracy and more uniform radiation dose distributions. Indirect evidence suggests that these improvements are reducing cardiac mortality. Direct evidence of the impact on quality of life is awaited from ongoing trials. Evidence relating to optimal radiotherapy dose fractionation is also awaited from on-going trials. The START trial was launched in March 1999, and a total of approximately 4000 patients is required over a period of five years.<sup>7, 8</sup> The UK appears to be lagging behind mainland Europe and the USA in the implementation of new technologies. Data from a quality assurance survey of the START trial show that 80% of radiotherapy departments are planning curative treatment without access to CT imaging of the breast, underlying heart or regional lymphatic pathways, or 3D planning systems (START Trial Quality Assurance Survey 1999, unpublished).

## 2. DCIS

### The Questions

- a. Does radiotherapy after breast conserving surgery for DCIS reduce the incidence of recurrence compared with local excision alone?
- b. For which patients with DCIS should radiotherapy after conservative surgery be recommended?

### The Nature of the Research Evidence

- a. Two systematic reviews have addressed several aspects of the management of DCIS, including whether radiotherapy should be offered following conserving surgery. One is current to April 2001,<sup>10</sup> (Grade I and III). The other review, conducted for the Australian NHMRC and published in 1998, is currently being updated as a Cochrane review.<sup>11</sup> The Canadian review is summarised in Table 5.

The UK, Australia and New Zealand RCT for the management of screen-detected DCIS compared the effectiveness of complete local excision alone with complete local excision followed by radiotherapy to the residual ipsilateral breast tissue (and/or tamoxifen). The findings have been submitted for publication.<sup>12</sup> A trial of postoperative radiotherapy versus control after conserving surgery for DCIS is being conducted in Sweden.<sup>13</sup>

- b. The same two systematic reviews as above addressed the question of which patients might be spared irradiation.<sup>10, 11</sup>

ECOG E5194 is an ongoing prospective cohort study of local excision alone in low/intermediate grade DCIS (less than 2.5cm) or high grade (less than 1cm, resected with greater than 3cm margins). The Radiation Therapy Oncology

Group (RTOG) is recruiting patients to an RCT of lumpectomy versus lumpectomy plus radiation in low/intermediate grade DCIS (less than 2.5cm, fully resected).

## Summary of the Research Evidence

- a. Published results from two RCTs were pooled in the Canadian systematic review.<sup>10</sup> In one RCT (NSABP B-17; n=814) radiotherapy following conserving surgery reduced the rate of ipsilateral invasive recurrence, at 8-years follow-up, from 13.4% to 3.9% (P=0.0001), and the rate of ipsilateral non-invasive recurrence from 13.4% to 8.2% (P=0.007).<sup>14</sup> At 4-years follow-up the EORTC (10853) trial (n=1010) showed a reduction in local invasive recurrence with radiotherapy from 8% to 4% (HR 0.60, 95% CI 0.37 to 0.97), and a reduction in local non-invasive recurrence with radiotherapy from 8% to 5% (HR 0.65, 95% CI 0.41 to 1.03).<sup>15</sup> The pooled relative risk for local recurrence was 0.53 (95% CI 0.37 to 0.75, P=0.0004; n=1824) in favour of conserving surgery plus radiotherapy (Grade I).

The EORTC trial reported a significantly higher rate of contralateral breast cancer with radiotherapy, whereas the NSABP trial reported a higher, but not statistically significant, difference in the same direction. The pooled relative risk for contralateral recurrence favoured patients who did not receive radiotherapy (RR 1.88, 95% CI 1.12 to 3.16, P=0.017; n=1816).

Using the same two RCTs (but shorter follow-up data available at that time), and 23 non-randomised studies (n=1349), the Australian review concluded in 1998 that conservative surgery with radiotherapy was associated with an intermediate level of local recurrence (8%) from either DCIS (4.3%) or invasive cancer (3.7%) at an approximate follow-up of 4½ years (Grade III). The review reports that there is a lack of reliable evidence of any reduction in risk of distant relapse with radiotherapy.

The UKCCCR DCIS working party has submitted for publication the findings from the UK, Australia and New Zealand RCT. As the data are unpublished they cannot be described here in detail. Women with completely excised DCIS were randomised to radiotherapy (n=118), tamoxifen (n=664) or tamoxifen plus radiotherapy (n=912). Median follow up data at 52.6 months indicated that radiotherapy significantly reduced the incidence of ipsilateral invasive recurrence and ipsilateral DCIS,<sup>12</sup> (D. George, personal communication, Grade II).

### **Pathological classification of DCIS**

Nine pathological features were evaluated in 623 patients from the NSABP-B17 trial in an attempt to predict risk of recurrence. The hazard rates for ipsilateral breast cancer were lower in all nine pathological characteristics in the lumpectomy plus radiotherapy group than in the lumpectomy alone group,<sup>10</sup> (Grade II).

Several pathology classification systems have been proposed to identify those lesions most likely to recur or progress to invasive cancer in women who have had conserving surgery. No system to date has been useful in predicting whether local disease is likely to recur as in-situ or invasive carcinoma. A consensus conference in 1997 on the classification of DCIS recommended that

the pathologist should clearly report the nuclear grade and the presence or absence of necrosis and cell polarisation, and state any specific grading system used. In general, greatest consistency among pathologists appears to be achieved using classification systems based on nuclear grade,<sup>10</sup> (Grade VII).

The Royal College of Pathologists provide minimum dataset guidelines for DCIS histopathology reports, including margins and size, which are consistent with current clinical evidence of the impact on treatment decisions.<sup>16</sup>

- b. The Canadian review found no published studies that randomised women at low risk of local recurrence to adjuvant radiotherapy versus observation. Patient series and cohort studies suggest that women at low risk of recurrence may not need adjuvant radiation (Grade III). Interpretation of these data is limited by the non-randomised historical comparisons and small patient subgroups evaluated.

In a consecutive patient series in which a defined DCIS pathologic classification was applied prospectively, high nuclear grade was shown to be the most important predictor of local recurrence in patients with DCIS treated with breast conservation (Grade VI). A subsequent cohort study applied a combined prognostic index score based on tumour size (less than 1.5, 1.6 to 4.0, greater than 4.1cm), margin width (less than 1, 1 to 9, greater than 10mm), and pathologic classification, a score of 1 (best) to 3 (worst) was assigned for each predictor. Women with DCIS treated with breast conservation (195 by excision only and 138 by excision plus radiotherapy) were followed-up for detection of local recurrence. The study showed no statistical difference in the 8-year local recurrence free survival in women with overall scores of 3 or 4 (low risk), regardless of whether or not radiation therapy was used. A score of 5, 6, or 7 (intermediate risk) was associated with a statistically significant 17% local recurrence free survival benefit with radiotherapy (85% versus 68%;  $P = 0.017$ ). Women with scores of 8 or 9 (high risk) showed the greatest relative benefit from radiotherapy but remained at substantial risk (in excess of 60%) of recurrence,<sup>10</sup> (Grade V).

A retrospective analysis of the pathological results of 213 women with DCIS who received radiotherapy after conserving surgery and 256 who had no further treatment, reported no benefit to radiation therapy in 8-year recurrence for patients with margins greater than 10mm ( $n=133$ ) or 1 to less than 10mm ( $n=224$ ). There was a significant benefit with radiation therapy for women with margins of less than 1mm (RR 2.54, 95% CI 1.25 to 5.18,  $P=0.01$ ;  $n=112$ ),<sup>10</sup> (Grade V).

The Australian review concluded that radiotherapy appears to be an appropriate treatment in reducing the risk of local recurrence of invasive cancer in women at sufficient risk, however, its overall role in the management of DCIS remains unclear (Grade III). The most important prognostic factors for local recurrence are margin involvement and moderate or marked comedo necrosis, based on an overview of the literature (not a systematic review).



### 3. Primary Breast Cancer

#### The Questions

- a. What is the effect on long-term survival and local recurrence of radiotherapy following mastectomy or conserving surgery for primary breast cancer?
- b. What is the optimum sequencing of chemotherapy and radiotherapy in the adjuvant treatment of early breast cancer?

#### Nature of the Research Evidence

- a. The Early Breast Cancer Trialists' Collaborative Group have published an individual patient data meta-analysis (Grade D) of 10-year and 20-year mortality results from 40 RCTs based on central review of individual patient data from 20,000 women, half with node-positive disease.<sup>17</sup> There is also a systematic review (Grade D) on the effects of locoregional radiotherapy on survival in women treated with conserving surgery.<sup>18, 19</sup> These reviews are summarised in Table 5.
- b. One systematic review (Grade I and III) looked at the question of optimal sequencing of adjuvant radiotherapy and chemotherapy.<sup>18, 19</sup> The optimum sequencing of chemotherapy and radiotherapy in the adjuvant treatment of early breast cancer is being addressed in a large RCT being conducted in the West Midlands.<sup>20</sup>

5

#### Summary of the Research Evidence

- a. The EBCTCG published meta-analysis is summarised in Table 5. Overall 20-year survival was not significantly improved, 37.1% with radiotherapy versus 35.9% without radiotherapy (2P=0.06), a survival difference of 1.2%. The absolute improvement in 10-year overall survival was 2.1%,<sup>17</sup> (Grade D).

The absolute risk of isolated local recurrence (as first event) at 20-years was 10.4% with radiotherapy versus 30.1% without radiotherapy (absolute difference 19.7%, SE 0.8; 2P<0.00001), based on 37 RCTs that reported site of first recurrence. Subgroup analyses indicated no substantial difference in proportional reduction in local recurrence among younger and older women (few women were older than 70 years), or among women with node-positive or node-negative disease, or according to whether adjuvant systemic therapies had been used or not (Grade D).

Overall there was a significant reduction in breast cancer deaths; in the absence of other causes of death the 20-year survival would have been 53.4% with radiotherapy and 48.6% without radiotherapy. After year two (breast cancer mortality did not appear to be reduced by radiotherapy in the first two years), on average, radiotherapy reduced annual mortality rates from breast cancer by 13.2% (SE 2.5), but increased deaths from other causes by 21.2% (SE 5.4). Regardless of primary surgery or adjuvant systemic therapies, the data suggests that the prevention of four isolated local-regional recurrences prevents one premature death from breast cancer at 20 years (Grade D).

Non-breast cancer mortality was significantly higher in the radiotherapy group, and appeared to involve an excess of deaths from vascular causes. Insufficient data were collected on cardiac exposure to radiation to determine whether the increase in vascular deaths was related to such exposure. The authors suggest that newer, potentially less harmful, radiotherapy regimens might benefit a wider range of women in terms of long-term survival. The Danish national trials (DBCG 82b and 82c, 3046 patients) reported a survival benefit which appears better than the overall average (10% at 12-years with radiotherapy compared to no radiotherapy), with no apparent excess of deaths from ischaemic heart disease (13 versus 12).<sup>21</sup> At 14-years follow-up there is still no evidence of adverse cardiac events with radiotherapy in these trials (M. Overgaard, personal communication). Special efforts were made to limit cardiac exposure in these trials. The numbers of vascular deaths is small, however, and follow-up too short to demonstrate long-term safety. Although reassuring, cardiac mortality still needs to be monitored very closely.

The Canadian systematic review covered the same trials as the EBCTCG in terms of the effectiveness of post-surgery radiotherapy, and the findings agree in terms of survival and local recurrence.<sup>18</sup>

The EBCTCG meta-analysis cannot determine the relative contributions to cure of local (breast/chest wall) radiotherapy and regional (axilla/supraclavicular fossa/internal mammary chain) radiotherapy. If a therapeutic dissection of the axilla has been performed, it may be argued that the curative role of radiotherapy to the axilla/supraclavicular fossa/internal mammary chain remains to be shown. There is an RCT underway of internal mammary and medial supraclavicular lymph node chain irradiation versus no further therapy in women with resected stage I/II/III breast cancer (EORTC 22922/10925).<sup>22-24</sup>

- b. A systematic review concluded that the optimal sequencing of chemotherapy and radiotherapy is unknown,<sup>18</sup> (Grade I/III).

Five-year results are published from one RCT of chemotherapy either before or after radiation therapy, conducted in 244 women following breast-conserving surgery for stage I or II breast cancer who were considered to be at substantial risk for systemic metastases.<sup>25</sup> Radiation before chemotherapy showed an increase in distant recurrence (36% versus 25%,  $P=0.05$ ), a lower rate of local recurrence (5% versus 14%,  $P=0.07$ ), but no difference in overall survival (73% versus 81%,  $P = 0.11$ ) (Grade II). Interpretation is limited because non-standard chemotherapy was used (cyclophosphamide, doxorubicin, methotrexate, 5-fluorouracil, prednisone) and some women received nodal radiation resulting in lower doses of chemotherapy in the radiation-first group.<sup>18</sup> The systematic review also described four cohort studies that examined the effect of sequencing chemotherapy and radiation therapy, none of which were conclusive (Grade III). Three case series provide some evidence for caution regarding the potential for increased adverse effects of radiotherapy when chemotherapy and radiotherapy are given concurrently, especially when anthracycline-based regimens are used,<sup>18</sup> (Grade III).

Data are awaited from the SECRAB trial.

**Table 5. Radiotherapy: systematic reviews**

Study, grade	Aims of study	Included studies	Outcome measures	Results	Comments
EBCTCG, 2000 <sup>17</sup> Grade I	To evaluate favourable and unfavourable effects on long-term survival of radiotherapy for breast cancer using individual patient data from RCTs.	40 RCTs (n=19 582) begun before 1990 that compared radiotherapy plus other treatments versus the same other treatments without radiotherapy.  Surgical interventions included mastectomy only, mastectomy with axillary sampling, mastectomy with axillary clearance, and conservative surgery with axillary clearance.	Mortality, time to local recurrence, time to distant recurrence.	Meta-analysis of all 40 RCTs showed that overall 20-year survival was 37.1% with radiation and 35.9% without (2P=0.06). There was an absolute improvement in survival at 10 years of 2.1%, but by 20 years the difference was only 1.2%.  Breast cancer mortality was significantly reduced with radiotherapy (2P=0.0001). On average, after year 2, radiotherapy reduced annual breast cancer mortality by 13.2% (SE 2.5). Radiotherapy increased mortality from other causes by 21.2% (SE 5.4), and vascular mortality particularly was increased.  The risk of isolated local recurrence of breast cancer was 10.4% with radiotherapy versus 30.1% without, an absolute difference in risk of 19.7% (SE 0.8, 2P=0.00001). Subgroup analyses showed similar proportional reductions produced by radiotherapy after the four different types of surgery. No difference was shown between younger and older women, or among women with node-positive or node-negative disease.	A thorough up-dated individual patient data analysis of a large data set, including appropriate subgroup analyses and exploration of heterogeneity.
Whelan 2001 <sup>18</sup> Grade I	To address the questions: Should breast irradiation be given to women with early breast cancer following conserving surgery? Is there an optimal schedule for breast irradiation? What is a reasonable interval between surgery and radiation? Can some patients be spared post-lumpectomy radiation?	1 meta-analysis of breast conserving surgery with or without breast irradiation (as above). <sup>17</sup> 4 RCTs comparing different fractionation schedules. 2 cohort studies on timing, plus indirect evidence from RCTs comparing treatment regimens. Case series were reviewed for morbidity data.	Survival, local recurrence rate, morbidity.	Mortality and recurrence results agree with the EBCTCG meta-analysis of individual patient data. Reduction in risk of local recurrence ranged from 73 to 89%. No survival impact.  Women at low risk of recurrence who might be spared irradiation cannot be identified based on the evidence reviewed; trials are on-going.  The optimum fractionation schedule has not been established and the role of boost irradiation is unclear.  A safe window between surgery and starting radiation therapy is not known.  The optimal sequencing of chemotherapy and radiotherapy is not known.  Major adverse effects of breast irradiation occur infrequently; the impact on quality of life has not been well studied.	A broad but thorough review of summary data, regularly updated.

Study, grade	Aims of study	Included studies	Outcome measures	Results	Comments
Wright 2001 <sup>10</sup> Grade I/III	<p>To address the questions:</p> <p>What is the optimal surgical management of DCIS?</p> <p>Should breast irradiation be offered following breast conserving surgery or lumpectomy?</p> <p>Are there patients who can be spared irradiation post lumpectomy?</p> <p>What is the role of tamoxifen?</p>	<p>Surgical management: 1 meta-analysis of 5 prospective and 9 retrospective studies and 10 clinical series (13/24 studies had no control group)<sup>26</sup>.</p> <p>Radiation following breast conserving surgery: Meta-analysis of 2 RCTs (8-year results from NSABP B-17, and 4-year results from EORTC 10853).</p> <p>Omission of radiation following breast conserving surgery: cohort studies and prospective series.</p> <p>Tamoxifen: 1 RCT of lumpectomy, radiation and tamoxifen versus lumpectomy, radiation and placebo (NSABP B-24).</p>	<p>Overall survival, disease-free survival, local recurrence, distant recurrence, quality of life.</p>	<p>Surgical management: meta-analysis of cohort studies and clinical series showed a higher, but not statistically significant, relative risk of local recurrence at 5 years in patients who had conserving surgery (with or without radiation) compared to those who had mastectomy (RR 2.86, 95% CI 0.77 to 7.56; n=1840 conserving surgery, 567 mastectomy). The result was similar when only conserving surgery plus radiation was compared with mastectomy (RR 2.16, 95% CI 0.69 to 5.41). No significant difference was found in the relative risk of mortality. Pooled analysis of treatments individually showed a lower estimated 5-year local recurrence rate in women who underwent mastectomy (4.6%, 95% CI 2.3 to 7.6) compared to conserving surgery with or without radiation (21.5%, 95% CI 14.0 to 30.7), but the probability difference was not significant. Conserving surgery plus radiation showed a similar estimated risk of local recurrence (10.6%, 95% CI 5.6 to 16.9) to mastectomy (7.3%, 95% CI 2.7 to 14.1). Estimated 5-year mortality was similar for conserving surgery (4.2%, 95% CI 1.4 to 8.5) and mastectomy (3.9%, 95% CI 1.7 to 6.8). Tests for homogeneity were not statistically significant, however, interpretation of the findings is very much limited by the design of the primary studies and cross-study comparisons in the meta-analysis.</p> <p>Breast irradiation following conserving surgery: Meta-analysis of 2 RCTs (n=1824) gave a relative risk (RR) of 0.53 (95% CI 0.42 to 0.66, P=0.00001) in favour of conserving surgery plus radiotherapy versus no radiotherapy for local recurrence. The RR for contralateral recurrence favoured patients who did not receive radiotherapy (1.88, 95% CI 1.12 to 3.16, P=0.017)</p> <p>Omission of radiation following conserving surgery: Cohorts and patient series suggest that the risk of recurrence may be identified by tumour size, margin width and pathological classification, and that low risk women may not benefit from adjuvant radiation. Interpretation is limited by the non-randomised historical comparisons and small patient sub-groups.</p> <p>Tamoxifen: an RCT (n=1084) of tamoxifen versus placebo, following lumpectomy and radiation, showed fewer breast cancer events at 5-years with tamoxifen (8.2 versus 13.4%, P=0.0009). A lower incidence rate in invasive recurrence (4.1% versus 7.2%, P=0.004), and a trend towards significance in non-invasive recurrence (4.2% versus 6.2%, P=0.08).</p>	<p>A thorough review which is updated regularly on the web and used to inform Canadian national practice guidelines.</p> <p>The findings from the meta-analysis<sup>26</sup> need to be interpreted with caution as it involved cross-study comparisons, non-randomised studies, and studies without comparison groups.</p>

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# Systemic Therapy

## 1. Endocrine Therapy for DCIS

### The Question

What is the role of tamoxifen in the management of DCIS?

### The Nature of the Research Evidence

Two systematic reviews have addressed the role of tamoxifen in DCIS, one conducted in Canada,<sup>1</sup> the other in Australia.<sup>2</sup> These reviews (Grade I/III) are summarised in Table 4a (Surgery).

The UK, Australia and New Zealand RCT for the management of screen-detected DCIS compared radiotherapy and tamoxifen (20mg daily for 5 years) in women with completely excised DCIS,<sup>3</sup> (Grade II).

The ongoing Radiation Therapy Oncology Group RCT (RTOG 98-04) in the US compares tamoxifen with or without radiation in women with DCIS who are considered at low risk of recurrence. Randomised participants have been stratified by margin extent, tumour size, and age.

### Summary of the Research Evidence

The Canadian review identified one RCT (NSABP B-24) for which results are published, and the Australian review did not identify additional evidence on this question. The RCT (NSABP B-24) of tamoxifen versus placebo following lumpectomy and radiation (n=1084) showed fewer breast cancer events (invasive and non-invasive) at 5-years with tamoxifen (8.2% versus 13.4%, P=0.0009). The incidence rate of invasive disease was significantly lower (4.1% versus 7.2%, P=0.004), whereas for non-invasive disease there was a non-significant trend towards lower incidence with tamoxifen (4.2% versus 6.2%, P=0.08). Five-year survival was similar in both groups. Patients given tamoxifen were at increased risk of endometrial cancer but the number of events was small, 7 in the tamoxifen group and 2 in the placebo group (RR 3.4, 95% CI 0.6 to 33.4) and the difference was not statistically significant (P=0.20).<sup>1, 4</sup> The findings from this trial in women who had a low risk of recurrence are alone insufficient to recommend the routine use of tamoxifen, and the absolute benefit needs to be weighed against the risk of developing endometrial cancer (Grade I).

Results from the UK, Australia and New Zealand RCT have been submitted for publication and so can not be given here in detail. Women were randomised to radiotherapy (n=118), tamoxifen (n=664) or tamoxifen plus radiotherapy (n=912). Median follow up data at 52.6 months indicated little support for the use of tamoxifen (D. George, personal communication, Grade II).

## 2. Neoadjuvant Therapy for Early Breast Cancer

### The Question

What evidence is there for primary neoadjuvant systemic therapy to down-stage tumour status in terms of the need for mastectomy, quality of life and survival?

### Nature of the Research Evidence

No systematic review was identified.

Neoadjuvant chemotherapy has been evaluated in four RCTs (Grade II). A large multicentre trial conducted in the US and Canada (NSABP B-18).<sup>5,6</sup> A trial conducted at The Royal Marsden Hospital in the UK.<sup>7,8</sup> Plus two French trials, one by the Institut Bergonie Bordeaux Groupe Sein,<sup>9</sup> and one from the Institut Curie.<sup>10,11</sup> These trials are summarised in Table 6b.

### Summary of the Research Evidence

In the NSABP B-18 trial women were assigned to preoperative (n=760) or postoperative (n=763) chemotherapy (plus radiotherapy if required; women aged 50 or over were also given tamoxifen).<sup>6</sup> The trial showed no significant difference in disease-free survival, distant disease-free survival or overall survival between neoadjuvant and adjuvant chemotherapy (Grade II).

Before treatment, approximately 28% of the women in both groups had tumours of less than or equal to 2cm, and 13% had tumours greater than or equal to 5.1cm. Preoperative chemotherapy reduced tumour size in 554 (80%) of the 693/747 evaluable patients who were assessable; 36% had a complete response and 44% a partial response. Pathological examination of breast tissue from 245 women who had a complete response following preoperative chemotherapy found no cancer in 26% and only non-invasive DCIS in 11%. Fifty-seven percent of women who received adjuvant chemotherapy were found at surgery to have positive axillary nodes compared to 41% in the neoadjuvant group (P<0.01). Women who received neoadjuvant chemotherapy were more likely to have a lumpectomy than women who had postoperative adjuvant chemotherapy (67.8% versus 59.8%, P<0.10). The rate of ipsilateral breast recurrence after lumpectomy was similar in both groups (Grade II).

In the Royal Marsden trial the main outcomes were clinical response to downstaging and the requirement for mastectomy. Before treatment 10% of neoadjuvant patients and 14% of adjuvant patients had a tumour size less than 2cm, following neoadjuvant chemoendocrine therapy, 79% had a tumour less than 2cm (P<0.0001). Similarly, a significant (P<0.0001) clinical downstaging of palpable nodes was seen, in the neoadjuvant group 32/149 had N1 node status pre-chemoendocrine therapy and only four post-chemoendocrine therapy. In the group who received neoadjuvant therapy, 10% (n=14) required mastectomy compared to 22% (n=31) in the adjuvant group (P<0.003). The other women had local excision followed by radiotherapy.<sup>7,8</sup> At a median follow-up of 48 months (range 10 to 70 months) no significant difference in survival or local or metastatic recurrence was found (Grade II).



The French Institut Bergonie Bordeaux Groupe Sein trial,<sup>9</sup> randomised 272 women with operable breast cancer larger than 3cm, to neoadjuvant chemotherapy followed by adjuvant loco-regional treatment, adjusted according to their response to chemotherapy, or, to initial mastectomy followed by adjuvant chemotherapy. The primary outcome was long-term survival (median follow-up 124 months, range 47 to 148). Survival rates were similar in both groups. Analysis of the first sites of relapse showed more locoregional recurrences among the neoadjuvant patients (31 women, 18 of whom later developed metastatic disease), compared with adjuvant therapy patients (12 women, 11 of whom later developed metastatic disease). (Grade II.)

The French Institut Curie trial,<sup>10, 11</sup> evaluated 390 women with tumours considered too large for breast conserving surgery (3 to 7cm), who received neoadjuvant chemotherapy (followed by local-regional treatment) (n=200), or induction radiotherapy with or without surgery, followed by adjuvant chemotherapy (n=190). The rate of breast conservation was similar in both groups (63% versus 62%). At 66 months follow-up (range 14 to 92) no difference was found in the 5-year probability of survival (84% with neoadjuvant treatment and 78% with adjuvant treatment, P=0.18). No significant difference was found between the two groups in the local recurrence free rate or metastasis free rate. (Grade II.)

The four trials differed in the type of neoadjuvant therapy used (the NSABP B-18 and UK trials used chemotherapy and endocrine therapy), the chemotherapy agents and dose (both French trials decreased the dose because of hematotoxicity), the sequence of treatments (in the Institut Curie trial the adjuvant group received primary radiotherapy, whereas initial treatment for this group in the other trials was surgery), primary outcome measure (recurrence and need for mastectomy in the UK trial, survival in the others). All the participants in the UK and NSABP B-18 trials received surgery, whereas participants in the two French trials who achieved complete clinical regression were treated with irradiation instead. It is, therefore, not appropriate to combine these trials.

### 3. Chemotherapy for Early Breast Cancer

#### The Questions

- a. Is there evidence from randomised trials that anthracycline containing multiple-agent adjuvant treatment improves quality of life and survival in women with breast cancer compared to CMF?
  - CMF versus AC
  - CMF versus FEC/FAC
  - CMF versus ECF
  - FEC versus ECF
- b. Does measurement of oestrogen and progesterone receptor status inform prescribing and improve the outcome of adjuvant chemotherapy?

- c. Is there a role for high dose chemotherapy with CMF in breast cancer treatment?
- d. What is the role for taxanes in the adjuvant treatment of breast cancer?

## Nature of the Research Evidence

- a. A systematic review (Grade I) of adjuvant prolonged polychemotherapy included individual patient data from 11 RCTs of anthracycline-containing regimens versus CMF.<sup>12</sup> This review is summarised in Table 6a.

The NSABP B-15 RCT of adjuvant anthracycline therapy (adriamycin and cyclophosphamide) versus conventional CMF reported some data on adverse effects and quality of life,<sup>13</sup> (Grade II).

An RCT sponsored by the Scottish Cancer Therapy Network (CRC-TU-NEAT, EU-98041) has compared adjuvant CMF with or without epirubicin in women with early stage breast cancer to assess survival, toxicity and quality of life. (The study started in October 1996, aims to recruit 1000 patients over 3 years and will follow-up annually for 10 years.)

An RCT sponsored by the Cancer Research Campaign Clinical Trials Centre (SCTN-BR9601, EU-97031) has compared CMF with or without epirubicin in women who have undergone surgery for early stage breast cancer to assess disease-free and overall survival and quality of life. (The study started in March 1996, aims to recruit 2000 patients over 4 years and will follow-up annually for 10 years.)

A small Czech trial (n=106) of CMF versus AC was reported as on-going in 1998,<sup>14</sup> as was a Nordic RCT of CMF versus CEF (DBCG 89 D).<sup>15</sup>

- b. No systematic review was identified. A trial in the UK randomised women to adjuvant CMF or no treatment, and compared patient outcomes according to ER (and c-erbB<sub>2</sub>) status.<sup>16</sup> A trial conducted in Japan randomised women to adjuvant chemotherapy, endocrine therapy, or chemoendocrine therapy, grouped by known ER (and menopausal) status to compare survival outcomes.<sup>17</sup> Progesterone status was not considered in these two RCTs. The relationship between ER and PR receptor status and clinical response to adjuvant treatment was investigated in a non-randomised study in Italy.<sup>18</sup> (Grade II and VI, studies not tabulated.)

A UK specialist group has recently published a practical protocol and scoring system for immunohistochemical detection of steroid receptors in breast cancer.<sup>19</sup>

- c. No systematic review was identified, and no RCTs were identified in addition to the eight trials discussed in recent reviews which, although not systematic reviews, appear to have captured the available randomised trials data (confirmed by an independent search for primary studies).<sup>20-22</sup>
- d. A systematic review has been undertaken to inform NICE guidelines on taxanes for advanced or metastatic breast cancer. None of the included trials evaluated adjuvant taxanes for primary breast cancer.<sup>23</sup>

Randomised trials of adjuvant taxanes for early breast cancer have produced preliminary analyses. The CALGB 9344 trial (n=3170) and the NSABP B-28 trial (n=3060) compared adriamycin and cyclophosphamide (AC) followed by paclitaxel (taxol) versus AC alone. The TACT trial of standard anthracycline-based chemotherapy with flurouracil, epirubicin and cyclophosphamide (FEC) versus FEC followed by sequential taxotere (docetaxel) is ongoing in the UK.

## Summary of the Research Evidence

- a. Meta-analysis of individual patient data from 11 RCTs showed superiority for adjuvant anthracycline chemotherapy over CMF (Grade I, Table 6a).<sup>12</sup> Compared with CMF alone, the anthracycline-containing regimens studied produced greater effects on recurrence (12%, SD 4, proportional reduction in recurrence, 2P=0.006), and mortality (69% versus 72% 5-year survival; log rank 2P=0.02). However, the 99% confidence interval reached zero and the results of several relevant trials are yet to become available. The results were similar for the 70% of women who were under 50 years of age at randomisation. Therefore, there may be moderate improvement in disease-free survival and overall survival with anthracycline therapy based on the 5-years follow-up. Follow-up is continuing. The EBCTCG published meta-analysis does not yet include direct randomised comparisons between different anthracycline-containing regimens, but this is planned for the next update.

The EBCTCG meta-analysis does not analyse adverse effects or quality of life. In the NSABP B-15 trial of adjuvant anthracycline chemotherapy, four cycles of AC (adriamycin and cyclophosphamide) treatment was completed on day 63 versus day 154 for six cycles of conventional CMF. Women visited health professionals three times as often for conventional CMF as for AC. Seventy-six percent of women treated with AC experienced vomiting (n=1492) compared to 39% given conventional CMF (n=739), and vomiting was likely to be more severe with AC. Women treated with conventional CMF experienced nausea without vomiting more frequently than women given AC. Nausea-control medication was given for about 84 days to CMF patients versus for about 12 days to AC patients. Alopecia occurred in almost all (92%) AC patients compared to 71% of women who received CMF,<sup>13</sup> (Grade II).

On the basis of the NSABP B-15 trial, which reported no difference in disease-free survival, distant disease-free survival, or overall survival, four cycles of AC is accepted as standard adjuvant therapy in the USA. In most of Europe six cycles are given on the basis that the extra two cycles might do good (J. Yarnold, personal communication). There is also variation in practice within the UK in the delivery of adjuvant CMF. A 1999 survey of 494 clinical and medical oncologists, of whom 434 (88%) responded, identified 36 regimens and 33 different dose-intensities being prescribed. The role of dose intensity in the outcome of CMF chemotherapy remains uncertain and there is a lack of research evidence to inform the debate.<sup>24</sup>

- b. In a Japanese RCT, ER-positive postmenopausal women (n=399) who received chemoendocrine therapy had significantly better relapse-free (P=0.04) and overall (P=0.019) survival compared with women who received tamoxifen or chemotherapy (mitomycin C and cyclophosphamide) alone (Grade II). No difference in outcomes was shown between endocrine therapy (oophorectomy and tamoxifen), chemotherapy, and chemoendocrine therapy among

premenopausal ER-positive women (n=462). In ER-negative women, postmenopausal (n=312) or premenopausal (n=318), no advantage was shown for tamoxifen in addition to chemotherapy alone. The median follow-up in this trial was 8.2 years (range 4 to 17.3 years).<sup>17</sup>

In a UK RCT, adjuvant CMF, compared with no treatment, improved relapse-free and overall survival for both ER-positive (n=207) and ER-negative (n=60) women,  $P<0.001$  in both cases (Grade II). ER-negative women showed the greatest benefit in overall survival (11.6 years with CMF, 2 years without,  $P<0.001$ ) compared with ER-positive women (11.3 years with CMF, 7.7 years without,  $P=0.01$ ). The median follow-up in this trial was 13.3 years (range 7.6 months to 16 years).<sup>16</sup>

A non-randomised Italian study of consecutive postmenopausal node-positive patients used statistical regression models to explore the relationship between ER and PR receptor status and disease-free survival response to adjuvant CMF (n=124) or tamoxifen (n=73). Univariate analysis suggested that neither ER nor PR was a significant prognostic indicator of disease-free survival in the group of women who received CMF, whilst ER, but not PR, was a significant prognostic indicator in the group who received tamoxifen ( $P=0.032$ ) (Grade VI). Further multivariate analysis of ER or PR status (along with age and number of positive nodes) in the CMF group was not appropriate. The median follow-up in this study was 146 months (range 6 to 173 months).<sup>18</sup>

A working protocol and scoring system for immunohistochemical detection of steroid receptors (ER and PR) in breast cancer has been suggested (Grade VII), although appropriate cut-off values for adjuvant treatment using steroid receptor determination by immunohistochemistry have yet to be determined.<sup>19</sup> The UK has a national quality assessment scheme for immunohistochemistry (UK NEQAS-ICC) with which over 200 laboratories are registered.<sup>25</sup>

- c. Three RCTs in advanced breast cancer and five of adjuvant treatment in high-risk patients so far do not provide sufficiently consistent or convincing evidence of an improvement in patient outcomes, compared to standard dose polychemotherapy, to inform recommendations on the use of high dose therapy,<sup>20-22</sup> (Grade II). Further follow-up of existing trials and reporting of ongoing and unpublished trials is needed before any change in practice should be considered, and until then high dose therapy strategies should not be offered outside of a randomised trial.
- d. The third interim report of the large CALGB 9344 trial (median follow-up 52 months) showed a significant reduction in the hazard of recurrence (13%) and death (14%) with adriamycin and cyclophosphamide (AC) followed by paclitaxel (taxol) compared with AC alone in women with ER-negative tumours. No difference was seen in ER-positive patients (NIH Adjuvant Breast Cancer Consensus Development Conference, November 2000). The NSABP B-28 trial results have been published in abstract (median follow-up 34 months). No significant difference was shown in disease-free survival or death (NIH Adjuvant Breast Cancer Consensus Development Conference, November 2000). In these trials the addition of paclitaxel extended the duration of adjuvant chemotherapy, which may be a confounding factor. In the UK TACT trial of docetaxel all participants in both treatment arms received the same number of cycles (eight). The TACT trial should be supported. In summary, consistent evidence to

support the use of taxanes as adjuvant treatment for early breast cancer, outside of a randomised trial, is lacking at this time.

## 4. Hormone Therapy for Early Breast Cancer

### The Questions

- a. What is the evidence from randomised trials to support aromatase inhibitors as part of adjuvant treatment regimens for newly diagnosed breast cancer?
- b. In pre-menopausal women with early breast cancer and ER+ tumours, does adjuvant therapy with a lutenising hormone-releasing hormone (LHRH) agonist (goserelin or buserelin) improve survival compared to CMF?
- c. In pre-menopausal women with early breast cancer and ER+ tumours who have maintained ovarian function following chemotherapy and tamoxifen therapy, does the addition of LHRH agonist therapy reduce the risk of recurrence?

### Nature of the Research Evidence

- a. There are as yet no published trials of aromatase inhibitors versus tamoxifen in the adjuvant setting although several trials are ongoing.<sup>26</sup> The first trial to address this was the CRC ATAC trial which started in 1998 (end date December 2008), to compare five years adjuvant anastrozole (Arimidex) treatment versus tamoxifen versus both in postmenopausal women. Seven thousand patients have been recruited internationally and the intention is to report on relapse-free survival and overall survival at 10-years follow-up. An RCT of five years adjuvant letrozole versus tamoxifen versus both in postmenopausal women with operable breast cancer is ongoing (BIGFEMTA trial, Breast International Group). Adjuvant aromatase inhibitors following tamoxifen treatment is also being evaluated in RCTs. The International Collaboration Cancer Group trial (ICCG-Trial) is comparing standard five years tamoxifen with three years tamoxifen followed by two years exemestane. An Austrian-German collaborative trial (ARNO) is testing five years tamoxifen versus two years tamoxifen followed by three years anastrozole. In the MA.17 international intergroup trial women who are disease-free after five years adjuvant tamoxifen have been randomised to an additional five years of letrozole treatment or placebo. The NSABP B-33 randomised trial is comparing two years exemestane treatment or placebo following five years adjuvant tamoxifen.
- b. No systematic review was identified. An Italian multicentre RCT has compared ovarian suppression (goserelin or oophorectomy or ovarian irradiation) plus tamoxifen versus CMF as adjuvant treatment in pre/perimenopausal women with ER-positive breast cancer (GROCTA 02),<sup>27</sup> (Grade II).

Four ongoing RCTs were identified (abstracts only). An international multicentre trial of adjuvant goserelin versus CMF in pre or perimenopausal women with node positive stage II breast cancer (ZEBRA).<sup>28</sup> A multicentre trial of goserelin and CMF in premenopausal women with node-negative, receptor positive breast cancer (CRC/GIVIO).<sup>29</sup> An international trial of goserelin versus CMF versus CMF followed by goserelin (IBCSG VIII).<sup>30</sup> An Austrian trial included a comparison of

adjuvant tamoxifen and goserelin versus CMF in premenopausal women with stage I and II hormone responsive breast cancer (ABCSG 5).<sup>31</sup>

- c. No systematic review was identified, nor any RCT in women who had maintained ovarian function following chemotherapy and tamoxifen therapy.

## Summary of the Research Evidence

- a. Data are awaited from ongoing trials of adjuvant aromatase inhibitors versus tamoxifen as first line endocrine therapy or as adjuvant therapy following tamoxifen. Trials are also still in progress to determine whether tamoxifen treatment should continue beyond five years, or whether substitution after five years by an aromatase inhibitor is beneficial. None of these trials will report for several years.<sup>26, 32</sup>
- b. In the Italian trial (GROCTA 02) the method of ovarian suppression was not randomised, but chosen by the local investigator or by the patient. Of 124 participants assigned to ovarian suppression, 87 received goserelin injections. The trial found no significant difference in disease-free or overall survival (median follow-up 76 months, range 9 to 121) between tamoxifen plus ovarian suppression (n=124) versus CMF (n=120),<sup>27</sup> (Grade IV). No difference was shown in clinical outcome between patients treated with oophorectomy (n=6) or ovarian irradiation (n=31) compared to those treated with goserelin (n=87). Fourteen (38%) women treated with oophorectomy or ovarian irradiation relapsed, compared to 29 (33%) of those treated with goserelin. There were six deaths among the 37 women treated with oophorectomy or ovarian irradiation compared to 12/87 in the goserelin group.

Interim findings from the ABCSG 5 trial (n=1,045) have been presented only in abstract.<sup>31</sup> At a median follow-up of 42 months, women treated with adjuvant tamoxifen and goserelin had a significant improvement in recurrence-free survival compared to CMF ( $P<0.02$ ), but there was no statistical difference in overall survival (Grade II). Three RCTs (ZEBRA, CRC/GIVIO and IBCSG VIII) have yet to publish their findings. The ZEBRA trial closed in 1996 with 1640 patients recruited.<sup>28, 33</sup> The CRC/GIVIO trial recruitment closed in 2000; the intended recruitment was 766 patients and analysis is planned in 2003 after the occurrence of 143 events.<sup>29</sup> The IBCSG trial VIII started in 1990 and by 1998 had recruited 1060 women out of a minimum intended 1200.<sup>30, 33</sup>

- c. No comparative data were found for LHRH agonist therapy in premenopausal women with ER-positive early breast cancer who had maintained ovarian function following chemotherapy and tamoxifen therapy. This highlights an important gap in the research literature.

**Table 6a. Chemotherapy for early breast cancer: systematic reviews**

Study, grade	Aims of study	Included studies	Outcome measures	Results	Comments
EBCTCG 1998 <sup>12</sup> Grade I	To review the evidence on recurrence and survival, using meta-analysis of individual patient data, from RCTs of adjuvant prolonged polychemotherapy in women with early breast cancer.  The review addressed which women derived most benefit, and which regimens were most effective.	Participants: women with early breast cancer (70% were aged under 50 years when randomised).  Intervention: The review included 11 RCTs of anthracycline containing (e.g. FAC or FEC) regimens versus CMF, and only these trials are described here.  Study design: Data were available for analysis from 5942 women in 11 RCTs that began between 1976 and 1989.	Recurrence, death.	Meta-analysis of individual patient data from 11 RCTs showed that anthracycline-containing regimens yielded a further 12% (SD 4) proportional reduction in recurrence, and a marginally significant further 11% (SD 5) proportional reduction in mortality compared to CMF. There was no significant heterogeneity between the 11 trials. The results were similar for the 70% of women who were under 50 years of age when randomised.  There was possibly some moderate improvement in disease-free survival (3.2%, SD 1.5, 2P=0.006) and overall survival (2.7%, SD 1.4, 2P=0.02) with the anthracycline-containing regimens, based on 5-year follow-up data. For mortality, however, the absolute extra benefit from anthracycline therapy could be anywhere from about zero to double the value observed at 5 years.	A thorough and regularly updated analysis of individual patient data.





**Table 6b. Neoadjuvant therapy for early breast cancer: primary studies**

Study, country, grade	Aims of study	Participants	Intervention	Outcome measures	Results	Comments
Fisher 1998 <sup>5</sup> USA and Canada (NSABP B-18) Grade II	To determine whether preoperative chemotherapy prolongs survival compared with the same chemotherapy given postoperatively.	1,523 women with operable breast cancer.  Tumours had to be moveable in relation to the underlying muscle and chest wall, and palpable axillary nodes could not be fixed to each other or to the neurovascular bundle. Women whose tumours had ulceration, erythema, skin fixation, peau d'orange satellite breast nodules, or parasternal nodules were excluded.	Neoadjuvant: Four cycles of adriamycin cyclophosphamide (AC) followed by surgery (n=760).  Adjuvant: Surgery (lumpectomy and axillary node dissection, or modified radical mastectomy) followed by four cycles of adjuvant AC (n=763).  Women who had lumpectomy also had radiotherapy. Women aged ≥50 years were given 5-years tamoxifen following adjuvant chemotherapy.	The primary outcomes were disease-free survival (DFS), distant disease-free survival (DDFS), and overall survival.  Secondary outcomes were clinical and pathological response, downstaging of axillary lymph nodes, and the rate of breast-conserving surgery.	The mean study time was 6 years.  No difference was shown in DFS (P=0.99), DDFS (P=0.70) or overall survival (P=0.83).  Neoadjuvant chemotherapy reduced tumour size in 80% of patients (554/693 assessable patients). 36% had a complete response and 44% a partial response. The overall response rate was 79%. 17% were considered to have stable disease and 3% progressive disease.  Pathology examination of breast tissue from 245 women who had a complete response to neoadjuvant therapy found no cancer in 26% and only non-invasive DCIS in 11%.  57% of women who received adjuvant chemotherapy were found at surgery to have positive axillary nodes compared to 41% in the neoadjuvant group (P<0.01).  Women who received neoadjuvant therapy were more likely to undergo lumpectomy (67.8%) compared to women who had adjuvant chemotherapy (59.8%, P<0.10). The rate of ipsilateral recurrence after lumpectomy was similar in both groups (7.9% versus 5.8% , P=0.23).	An RCT, allocation concealment and blinding not reported. 1,495 (98%) patients were included in the analysis (743 neoadjuvant, 752 adjuvant). 9/1504 eligible women had no follow up. 13 neoadjuvant and 6 adjuvant were excluded from the analysis, reasons given.  Similar results were obtained when ineligible patients were included in the analysis.
Makris 1998 <sup>7</sup> UK (The Royal Marsden Trial) Grade II	To evaluate the role of neoadjuvant chemoendocrine therapy prior to surgery in primary operable breast cancer.	309 women, <70 years, with primary breast cancer and suitable for primary surgical treatment and systemic chemotherapy.  Excluded were women with evidence of metastasis, inoperable tumours for which chemotherapy or hormonal therapy were the initial treatment of choice, evidence of myocardial dysfunction, and premenopausal	Neoadjuvant: 4 cycles of chemoendocrine therapy (CET) prior to surgery and four courses after surgery, plus RT if required (n=157).  Adjuvant: 8 cycles of CET after surgery, and radiotherapy if required (n=152).  286 women were treated as per protocol, 144 neoadjuvant and 142 adjuvant.  CET comprised	The main outcomes were the effect of clinical response on downstaging (tumour stage and size) and the need for mastectomy.  Local and metastatic relapse, overall survival, and adverse effects were also assessed.	Median follow-up was 48 months (range 10 to 70).  Clinical response to neoadjuvant therapy: complete response 32/149 (21%); minimal residual disease 41 (28%); partial response 47 (32%); no change 22 (15%); progressive disease 2 (1%).  Before treatment 10% of the neoadjuvant group and 14% of the adjuvant group had tumours <2cm. After neoadjuvant therapy, 79% had a tumour <2cm (P<0.0001). A similar clinical downstaging of palpable nodes was seen, 32/149 had N1 status before neoadjuvant therapy, 4 were N1 after treatment (P<0.0001).  16/149 (11%) women in the neoadjuvant group required mastectomy compared to 31/144 (22%) in the adjuvant group (P<0.004) The remainder had local excision followed by RT. (Surgical requirement was measured at a	An RCT, allocation concealment and blinding not reported. Unclear if the analysis of clinical downstaging was to compare neoadjuvant with adjuvant treatment, or pre versus post neoadjuvant treatment. Evaluable patients were analysed, except for neoadjuvant response where only treated patients were included.



Study, country, grade	Aims of study	Participants	Intervention	Outcome measures	Results	Comments
		women who wished to consider pregnancy.	mitoxantrone, methotrexate (some women also received mitomycin C) and tamoxifen.		different time point in each group.) There was no significant difference shown in local relapse, metastatic relapse or overall survival. Symptomatic and haematologic acute toxicity was similarly low for neoadjuvant and adjuvant therapy.	
Mauriac 1999 <sup>9</sup> France (Institut Bergonie) Grade II	To evaluate whether neoadjuvant chemotherapy improves overall survival compared to adjuvant chemotherapy.	272 women with T2>3cm or T3 N0-1, M0 breast tumours. All had oestrogen and progesterone receptor status determined. Excluded: T4 tumours, N2/N3 nodes, bilateral cancer, slow growing tumours, other neoplasms, refusal of mastectomy or chemotherapy, contra-indications to chemotherapy or anaesthetic, plurifocal lesion, colloid tumour.	Neoadjuvant: chemotherapy followed by locoregional radiation. Lumpectomy was performed for tumours <2cm, mastectomy if residual tumour >2cm (n=134). Adjuvant: mastectomy followed by chemotherapy (n=138). (32 did not receive chemotherapy.) Chemotherapy was epirubicin, vincristine, methotrexate and mitomycin.	Overall survival (OS), recurrence free survival (RFS), and metastasis-free survival (MFS). Prognostic factors which might predict response to neoadjuvant chemotherapy and subsequent survival were investigated.	Median follow-up was 124 months (range 47 to 148 months). In the neoadjuvant group (n=134), 44 women (33%) had radiation alone, 40 (30%) had conserving surgery and breast radiation, and 49 (37%) had mastectomy. In the adjuvant group, all women had mastectomy and 75% (n=104) received adjuvant chemotherapy. No difference was shown in survival between the neoadjuvant and adjuvant groups. Analysis of the first sites of relapse showed more locoregional recurrences in the neoadjuvant group (31 women) than in the adjuvant group (12 women). 18 of the 31 women in the neoadjuvant group and 11 of the 12 women in the adjuvant group who had an initial isolated locoregional recurrence later developed metastatic disease.	An RCT, allocation concealment and blinding not reported. Chemotherapy dose reduction according to clinical and haematological toxicity was applied to 61 patients.
Scholl 1997 <sup>10, 11</sup> France (Institut Curie) Grade II	To assess whether prolonged (four cycles) neoadjuvant chemotherapy improves survival compared to the same chemotherapy after locoregional radiation, in premenopausal women with clinically node-positive or node-negative breast cancer.	414 premenopausal women with non-metastatic operable breast cancer (T2-T3, N0-N1, M0). Excluded were women with prior cancers, serious concomitant illness, tumours <3cm, bilateral, inflammatory or locally advanced breast cancer (>7cm).	Neoadjuvant: Four cycles of cyclophosphamide, doxorubicin, 5-fluorouracil (CAF), followed by radiation and surgery if persistent tumour (n=200). Adjuvant: the same CAF chemotherapy following locoregional radiation, and surgery if persistent tumour (n=190). Surgery was withheld in about half of the cases in each group.	The primary endpoint was survival. Disease-free interval, local recurrence rate, metastatic-free interval, breast conservation rate, and adverse events were also assessed.	Median follow-up 66 months (range 14 to 92). No difference was shown in the 5-year probability of survival, 84% (78 to 90) in the neoadjuvant group and 78% (72 to 84) in the adjuvant group (P=0.18). No difference was shown in the local recurrence free rate (74% in the neoadjuvant group and 80% in the adjuvant group, P=0.2) or in the metastasis-free rate (72% versus 65%, P=0.09). The rate of breast conservation was similar in both groups (63 versus 62%). Mastectomy was performed in 18% of patients who received neoadjuvant therapy and in 23% of adjuvant-treated patients.	An RCT, allocation concealment and blinding not reported. Protocol violations or randomisation errors affected 7 neoadjuvant and 12 adjuvant patients. On average, the neoadjuvant group had more intensive chemotherapy, but fewer treatment courses. Two neoadjuvant and 24 adjuvant patients did not receive chemotherapy.

## References for topic 6

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# Follow-Up After Treatment for Early Breast Cancer

## 1. Management of Lymphoedema

### The Questions

- a. What are the treatment related factors that predispose women with breast cancer to lymphoedema?
- b. How does lymphoedema following treatment for breast cancer (mastectomy, breast conserving surgery, axillary dissection, radiotherapy) affect quality of life?
- c. Is lymphoedema still a problem for women treated for breast cancer in the UK?
- d. What information on lifestyle do women need to minimise the impact of lymphoedema?
- e. What impact do different treatment options for management of lymphoedema have on quality of life, and when is the best time to start treatment?

### The Nature of the Research Evidence

- a. An RCT of management of the axilla in operable breast cancer assessed morbidity to the shoulder and arm associated with breast conservation surgery, the extent of axillary dissection, and radiotherapy to the axilla. This trial (the Edinburgh trial) is summarised in Table 7b.<sup>1</sup> A UK study which reported on the prevalence of arm oedema following treatment for breast cancer presented data according to treatment received,<sup>2</sup> (Grade VI, study not tabulated). Anecdotal evidence is available from the experience of nurse specialists (Grade VII).

Antibiotic prophylaxis against wound infection in patients undergoing primary breast surgery has been addressed in only two clinical trials (Grade II) published in 1990, according to a recent report,<sup>3</sup> and no later RCTs were identified.

- b. A study in the USA used cancer registry data to define the incidence of lymphoedema following axillary lymph node dissection and went on to investigate the effects of lymphoedema on quality of life,<sup>4</sup> (Grade VI). An earlier study from a UK lymphoedema clinic assessed psychological morbidity in women with arm swelling (attending between 1990 and 1991) compared to a matched control group who had received the same type of treatment but did not have arm swelling,<sup>5</sup> (Grade V). A study in Finland followed a consecutive series of women who underwent conserving surgery or mastectomy to find out how symptoms including oedema of the ipsilateral arm developed during the year

after treatment, and the impact of those symptoms on daily life,<sup>6</sup> (Grade IV). These studies are summarised in Table 7b.

Anecdotal evidence is available from the experience of specialist nurse carers (Grade VII).

- c. Some data were published in the mid-1990s, and more recent anecdotal figures from professionals in the field are available. Two studies (Grade VI) published in 1996, one based on questionnaire-collected data and the other on database data, reported on the prevalence of arm oedema and referral rates to specialist lymphoedema services in the UK.<sup>2,7</sup> An overview of the literature (reported to be systematic but lacking details of the methods used), published in 1995, estimated the incidence and prevalence of lymphoedema in women treated for breast cancer.<sup>8</sup>
- d. A questionnaire survey has described what 72 women treated for breast cancer in the USA knew about upper extremity lymphoedema, what they recalled being told to help prevent it, and what preventive and management strategies they used,<sup>9</sup> (Grade VI). The UK Lymphoedema Support Network has produced fact sheets for patients, as have similar agencies in other countries (Grade VII).
- e. There are a large number of small, poor quality, heterogenous studies that compare many different treatments and combinations of treatments. It is not possible to derive any meaningful conclusions from these studies as to the relative impact of each approach on patient outcomes. It is acknowledged among professionals in the field that there is very little evidence to support a conclusive statement on these issues which have already been identified as subjects for research within the Leeds Teaching Hospitals Trust (C. Lane, J. Todd, personal communication). Therapies which are generally used within the NHS include compression bandaging, drainage, liposuction, and physiotherapy. A systematic review has examined the effectiveness of physical therapies in the management of lymphoedema,<sup>10</sup> and meta-analysis has been used to evaluate the best time (early or delayed) to start physiotherapy following axillary dissection for breast cancer.<sup>11</sup> Neither of these reviews reported on quality of life (Grade I/III, Table 7a). No research studies were identified regarding liposuction.

## Summary of the Research Evidence

- a. Surgical axillary clearance was associated with significant upper limb lymphoedema in an RCT that compared axillary node sample (with or without radiotherapy, radiotherapy was not randomised) versus axillary clearance, in women treated with breast conserving surgery.<sup>1</sup> Women who had node sampling and no radiotherapy to the axilla had least morbidity of the shoulder and arm (Grade II). Following axillary clearance there was an early mean increase in arm volume of 4% that remained constant over the next 2.5 years, compared to a 2% increase with axillary sampling which improved with time. After 3-years, forearm circumference was significantly greater in women who had axillary clearance compared to those who had sampling alone (P=0.005) or sampling and radiotherapy (P=0.04) (actual size not reported). Radiotherapy to the axilla after node sampling also resulted in a significant reduction in range of shoulder movement. The authors concluded that women who are node negative after axillary sampling can avoid radiotherapy or axillary clearance, and

thereby suffer less shoulder and arm morbidity (the trial found no difference in recurrence or survival at a median follow-up of 4.1 years).

In 1996, data were published on the prevalence of chronic arm oedema among all 1249 women treated for breast cancer (but without tumour recurrence) living in the Worthing District Health Authority area.<sup>2</sup> Of 1077 women treated for unilateral breast cancer, 302 (28%) reported arm swelling (Grade VI). There was a significant ( $P=0.01$ ) increase in prevalence with time since treatment in women who received post-operative radiotherapy. Overall, arm oedema was twice as common among women treated by radiotherapy (type of surgery adjusted OR 2.45, 95% CI 1.86 to 3.27), and among patients treated with mastectomy compared to lumpectomy (radiotherapy adjusted OR 2.13, 95% CI 1.13 to 4.43).

An Oncology Divisional Nurse and a Macmillan Lymphoedema Specialist have observed that axillary dissection, radiotherapy in high doses especially to the axilla, and oblique surgical incision predispose patients to lymphoedema (Grade VII, C. Lane, J. Todd, personal communication). Neither of two RCTs ( $n=118$  and  $606$ ) of antibiotic prophylaxis against wound infection in patients undergoing primary breast surgery showed a significant reduction in wound infections (Grade II, not tabulated).<sup>3</sup>

- b. A case-control study in the UK is reported to be the first controlled study to have evaluated psychological morbidity of breast cancer related arm swelling.<sup>5</sup> In this small study (50 patients and 50 matched controls), women with arm lymphoedema were more likely to have some functional impairment both in relation to the swollen arm and overall functioning, compared to women who had received the same type of treatment for breast cancer but who did not have arm swelling. Women with arm lymphoedema had significantly poorer overall psychosocial adjustment to their illness and greater psychological morbidity (Grade V).

A review of one US hospital's registry data (1990 to 1996) showed that 8.3% (68/827) of patients who had axillary lymph node dissection as part of their treatment developed lymphoedema. A consecutive series of women who had undergone breast surgery (simple or modified radical mastectomy, lumpectomy or lumpectomy with axillary node dissection) completed a quality of life questionnaire (SF-36). Women who had developed lymphoedema following their surgical treatment had significantly lower scores for emotional aspects and bodily pain, compared to those who did not develop lymphoedema,<sup>4</sup> (Grade VI).

Twenty percent of women (19/93) in a small prospective study in Finland reported having lymphoedema in their ipsilateral arm one year after surgery. Actual measurement of the change in arm circumference pre- to post-operatively demonstrated lymphoedema in 38%, as defined by an increase of at least 2cm. Arm lymphoedema was observed more commonly in the mastectomy group than among women who underwent breast conserving surgery. The study found no significant correlation between the number of symptoms in the ipsilateral arm (sensory disturbance, grip strength, muscle weakness) and any measured levels of anxiety or depression,<sup>6</sup> (Grade IV).

An Oncology Divisional Nurse and a Macmillan Lymphoedema Specialist have observed that lymphoedema decreases the quality of life for women treated for

breast cancer (Grade VII) through pain and discomfort, anxiety and depression, greater functional impairment, poorer adjustment to their illness, difficulties with domestic environment and with relationships, feelings of resentment and embarrassment, poor body image, sexual dysfunction, and loss of self-value (C. Lane, J. Todd, personal communication). The research evidence generally supports these observations, although studies are few and of variable quality.

- c. Data collected in the Worthing District Health Authority in 1996 showed that of 1077 women treated for unilateral breast cancer, 302 (28%) reported arm swelling (Grade VI).<sup>2</sup>

Database data were published concerning 714 patients referred during a 5-year period (1989 to 1993) to a specialist lymphoedema service in Oxford.<sup>7</sup> The annual number of new patients almost doubled from 103 to 195. In addition to initial assessments, there were over 1000 follow-up appointments per year. Most patients were seen as out-patients and 84% of referrals were female. The main cause of lymphoedema was cancer and cancer treatments (68%). After two years, only 15% of patients were still attending the clinic regularly (Grade VI).

An overview of the literature published between 1981 and 1993 (Grade VI) reported that the prevalence rate of lymphoedema in women treated for breast cancer was in the region of 25 to 28%. According to the authors, approximately 30 000 women in England and Wales would be experiencing some degree of lymphoedema at the time of publication.<sup>8</sup>

Specialist carers have observed that patient numbers and new referrals to lymphoedema services continue to increase (C. Lane, J. Todd, personal communication, no data), and The Lymphoedema Support Network (for patients) say that from their perspective lymphoedema is still a problem as they continue to receive an increasing number of enquiries from patients (personal communication, no data). (Grade VII.)

- d. Little research has been conducted in this area. Several agencies, including The UK Lymphoedema Support Network, produce fact sheets on lymphoedema for breast cancer patients. These include precautions that women should take to reduce their risk of developing arm lymphoedema, which as one recent overview points out, that although logical these precautions are not based on research.<sup>12</sup>

A questionnaire survey conducted in a survivor-established breast cancer resource centre in the USA found that most of the 72 respondents were aware of their risk of lymphoedema, but that their knowledge and use of preventive strategies was poor,<sup>9</sup> (Grade VI). The reported use of consensus-based preventive strategies was similarly low among the 27 women who developed arm lymphoedema (0 to 48 months after treatment) and the 45 women who did not. The authors concluded that more research is needed to support or refute the lymphoedema prevention strategies currently being recommended.

- e. Good quality research evidence in this is lacking. There are many small studies which have looked at many different regimens such that data synthesis is impossible, and notably quality of life has rarely been considered as an important outcome. Neither has quality of life been considered in the systematic reviews identified. One systematic review of physical therapies concluded that some combination modalities show promise, but that the primary research is not



of good quality (Table 7a).<sup>10</sup> The only RCT (n=74) included in the review indicated that compression garments can reduce arm size after 6 months of use, but the impact of such garments on patients' quality of life was not measured. Another even smaller RCT (n=40) published in the same year as the review, and not included in the review, reported that a pressure garment did not reduce post-operative drainage, but the quality of the report of this trial is very poor.<sup>13</sup> Returning to the systematic review by Megens, complex physical therapy (a combination of compression bandaging/garment, exercise, massage and skin care) was supported (based on measurement of arm size) by two cohort studies, one of which advocated the use of compression garments rather than bandaging (Grade III). A compression garment in combination with microwave treatment showed promising results in one non-randomised study. There was no evidence found that elevation alone was effective. These studies are all very weak and the authors of the review concluded that more rigorous research was needed.

A meta-analysis of six RCTs showed a better outcome for wound drainage volume and duration when physiotherapy was started five to seven days after axillary dissection for breast cancer, rather than within two days (Grade D),<sup>11</sup> Three trials showed no significant difference in range of motion two to four weeks after the operation, and four trials reported no difference four to six months after the operation (meta-analysis was not possible because the trials assessed this outcome at different times and defined full range of motion in different ways). There were insufficient data for analysis of wound infection and seromas. Quality of life was not addressed in the review.

## 2. Hormone Replacement Therapy

### The Questions

- a. Should women with a history of breast cancer be offered HRT?
- b. Is routine (single-shot) mammography effective for early detection of breast cancer in women under the age of 50 years prior to HRT?

### The Nature of the Research Evidence

- a. There is a systematic review of oestrogen replacement therapy or combined oestrogen and progesterone replacement therapy (ERT/HRT) on the risk of breast cancer and other health risks and benefits in postmenopausal women, that focuses on women with a previous diagnosis of breast cancer,<sup>14</sup> (Grade III, Table 7a). There is a more recent report of a prospective observational study of ERT compared to no hormone therapy following breast cancer,<sup>15</sup> (Grade VI, study not tabulated).

There are several ongoing RCTs of HRT in women previously treated for breast cancer.

The antidepressant venlafaxine has been tested in a placebo controlled RCT as an alternative to hormone treatment for the management of hot flushes, and the report mentions three ongoing RCTs of other related antidepressants (paroxetine, fluoxetine, sertraline) for the same purpose.<sup>16</sup>

- b. No systematic review was identified and primary research on pre-HRT mammography for premenopausal women is scarce.

Data on mammography detection of breast cancer in women starting hormone replacement therapy have been collected in a UK Breast Unit.<sup>17</sup> In this study forty-five percent of women were younger than the National Screening Programme age (Grade VI).

In 1993 The Royal College of Radiologists issued a consensus statement (Grade VII) on hormone replacement therapy and mammography, and those views have been maintained in more recent RCR guidelines for doctors.<sup>18, 19</sup>

## Summary of the Research Evidence

- a. This remains a controversial issue because of the link between oestrogen and breast cancer and the fear of activating occult disease. A systematic review (Grade III) reported that data regarding ERT/HRT in women with breast cancer are scarce.<sup>14</sup> The authors found no RCTs. Data from case series, case control studies and case reports did not suggest a major detrimental effect of ERT/HRT in women with a previous diagnosis of breast cancer in terms of recurrence or breast cancer related deaths (Table 7a). The studies reviewed were not randomised, included few women, and had limited follow-up. The authors concluded that the balance of risks and benefits needed to be explored in RCTs.

A more recently published observational study,<sup>15</sup> (Grade IV) investigated whether ERT altered the development of new or recurrent breast cancer in women previously treated for localised breast cancer. Three-hundred and nineteen women (potential participants in an RCT) were observed prospectively for at least 2 years, 39/319 were given ERT and 280 were not given hormones. One patient in the ERT group (1/39) developed a new ER-positive breast cancer 72 months after a diagnosis of an ER-negative breast cancer, and 27 months after beginning ERT. In the control group, 14/280 women developed new or recurrent breast cancer at a median time of 139.5 months after diagnosis. The authors concluded that ERT did not increase breast cancer events in this subset of patients, and that RCTs were needed.

Among the ongoing RCTs, one is a UK multicentre trial in women with a history of early stage breast cancer, which compares HRT with giving advice on alternatives (including clonidine, venlafaxine, evening primrose oil, reflexology, acupuncture and massage). This trial was launched in October 2001 and aims to recruit 3000 women. The outcome measures are disease-free and overall survival, and quality of life. Another trial evaluates the safety of HRT, in terms of risk of recurrence, in women with previously treated, non-recurrent early (stage 0-II) breast cancer (IBCSG-17-98, EU-98077). This trial compares HRT with symptomatic use of non-hormonal therapies (clonidine, beta blockers, psychological support, physical exercise, acupuncture) and measures quality of life as well as breast cancer outcomes. There is also mention in the literature of an ongoing Nordic trial (SBG 9701) which randomised women to HRT or observation (including symptomatic treatment with clonidine or beta blockers) for 2 years.

The RCT of venlafaxine tested 4-weeks treatment with three different doses of the drug versus placebo (study not tabulated). Venlafaxine reduced the daily

hot flush activity by between 37% and 61% in the three dose groups, compared to a 27% reduction recorded in the placebo group. However, side effects including mouth dryness, decreased appetite, nausea and constipation were higher with venlafaxine. Confirmation of these results is awaited from three ongoing trials of related antidepressants.<sup>16</sup>

A booklet for patients on Breast Cancer Hormones and HRT has been produced by Cancer Support and Information, Lynda Jackson Macmillan Centre, published through Mount Vernon Hospital (1998). This states that the use of HRT in women who have had breast cancer is still controversial, and that more research is needed to assess how big the risks and benefits are. That statement appears still to be appropriate until the results from ongoing trials become available.

- b. A UK Breast Unit (at the Leeds General Infirmary) has collected data (Grade VI) on mammography in women on or starting hormone therapy, including women under 50 years not already on HRT.<sup>17</sup> Published data report that pre-HRT mammograms found 31 cancers in 5436 women (5.7 cancers per 1000 women screened) considering or already on HRT who had been referred for mammography outside the National Screening Programme. The benign/malignant final diagnosis was 1:1. Forty-five percent of the women in this series were outside the National Screening Programme screening age. The authors are continuing to collect data, and had by the end of the year 2000 detected 36 cancers in women about to start HRT or who had just started it and were asymptomatic (G. Parkin, personal communication). Of these 36 women, seven were under 50 years of age. Another 5/36 were under 52, although the National Screening Programme nominally starts at age 50 the first mammogram could fall anywhere between the 49<sup>th</sup> and 52<sup>nd</sup> birthday as the programme has a 3-year screening cycle.

A consensus statement from The Royal College of Radiologists in 1993 stated that commencement of HRT is not an indication for baseline mammography, and that routine mammography outside the National Screening Programme is not justified,<sup>18</sup> (Grade VII). However, whether mammography is able to detect occult breast cancers, and therefore prevent the administration of oestrogens to potentially oestrogen dependent tumours has been ignored in the several editions of the Royal College of Radiologists' guidelines, and their recommendations are challenged by the data from Leeds.



**Table 7a. Follow-up: systematic reviews**

Study, grade	Aims of study	Included studies	Outcome measures	Results	Comments
Megens, 1998 <sup>10</sup> Grade I/III	To review the research literature on physical therapist management of lymphoedema secondary to breast cancer treatments.	1 RCT, 5 non-randomised pre-test post-test cohort comparisons, 7 case series (1980 to 1996).  Interventions included complex physical therapy, massage, exercise, arm elevation, compression garments, ultrasound, pneumatic pump, electrical stimulation.	Difference in arm circumference, water volumetry.	Compression garments might reduce arm size after 6 months of use (1 RCT, n=74), pneumatic pumps or electrical stimulation do not improve results (1 cohort study).  Elevation alone was not shown to be an effective way to control lymphoedema (1 cohort study, no control group).  Microwave treatment in combination with compression garment showed promising effects on arm volume in one non-randomised study (n=45, pre-test/post-test design).  Complex physical therapy was supported by 2 cohort studies; one suggested that twice weekly treatment and compression garments rather than bandaging was sufficient	This review applies a thorough approach to evidence-based recommendations, although language and publication bias is possible.  The authors concluded that more rigorous research is needed to clarify the findings.
Roy, 1996 <sup>14</sup> Grade III	To review the literature on the risks and benefits of oestrogen replacement therapy (ERT) and hormone replacement therapy (HRT) in post-menopausal women, particularly those with a previous diagnosis of breast cancer.	Studies in women with a previous diagnosis of breast cancer were 3 case series, 2 case control studies and 2 case reports (published between 1988 and 1995). There were no RCTs in this patient group.	Included studies reported menopausal symptoms and breast cancer recurrence	Of the 3 case series, one in which treatment with HRT lasted 3 to 6 months found no cases of tumour reactivation over 2 years follow up (n=65); another reported 7 cases of recurrence among 77 women treated with ERT/HRT for an average of 27 months; in the third study 2/35 women relapsed over a mean follow up of 43 months after a mean duration of ERT and tamoxifen treatment of 14.6 months. These studies all used different treatment regimens.  Of the 2 case control studies, one reported cancer related deaths in 1/25 patients and 2/50 matched controls over 2 years follow up. Data from the other study were unpublished and showed significantly fewer recurrences in the HRT group of 90 patients compared to matched controls (details not given).  The contribution of ERT/HRT to breast cancer recurrence or progression in case reports is impossible to determine.	A fair quality review. The authors concluded that data regarding ERT/HRT in women with breast cancer are scarce, and that any observations from the studies included in this review must be viewed as preliminary.

Study, grade	Aims of study	Included studies	Outcome measures	Results	Comments
Schinkelshoek, 1998 <sup>11</sup> Grade I	To evaluate the best time (early or delayed) in the acute post-operative period to start physiotherapy for patients who have undergone axillary dissection for breast cancer	6 RCTs (n=257) and 1 non-randomised trial (n not reported).  Interventions were early (1 to 2 days postoperative) and late start physiotherapy (5 to 7 days post-operative).	Wound drainage volume, wound drainage duration, range of motion, presence of wound infection and seromas.	Meta-analysis of 5 RCTs showed that starting physiotherapy 5 to 7 days after surgery resulted in a significantly smaller wound drainage volume (mean difference 101.5 ml, 95% CI 94.91 to 108.1; effect size 0.35, 95% CI 0.17 to 0.53) and wound drainage duration (mean difference 0.93 days, 95% CI 0.41 to 1.47; effect size 0.37, 95% CI 0.17 to 0.57) compared to starting therapy within 2 days of surgery.  Range of motion in 6 RCTs could not be pooled because of differences in the time it was assessed and how full range of motion was defined. Three trials showed no significant difference 2 to 4 weeks post-operation, and four trials found no difference 4 to 6 months after the operation.  There was insufficient data for pooled analysis of wound infection and seromas	A reasonable quality review of trials published between 1979 and 1990, but only one database was searched. The inclusion criteria were explicit, studies were quality assessed, and the analysis was appropriate.

**Table 7b. Follow-up: primary studies**

Study, country, grade	Aims of study	Participants	Intervention	Outcome measures	Results	Comments
Chetty, 2000 <sup>1</sup> UK Grade II	To compare the efficacy of axillary node sample or clearance in women with operable breast cancer treated by breast conservation, and to assess the morbidity associated with these procedures and radiotherapy.	466 women aged under 70 years, with operable breast cancer and no evidence of metastatic disease.	Axillary clearance or axillary node sample.  Initially, all node sample patients were given radiotherapy (n=54), later only node-positive women were given radiotherapy. Radiotherapy was not given to women who had axillary clearance.	Recurrence and survival.  Morbidity of the shoulder and arm before and after operation was also assessed (limb volume and circumference, movement and muscle power).	Median follow-up was 4.1 years.  No difference was shown in time to axillary recurrence (P=0.94), breast cancer recurrence (P=0.97), overall 5-year survival (P=0.2) or disease-free survival (P=0.68).  Morbidity was assessed in 324 women and was least in those who had a node sample and no radiotherapy to the axilla. After axillary clearance there was an early mean increase in arm volume of 4% that remained constant over the next 2.5 years, compared to a 2% increase with axillary sampling which improved with time. At 3-years forearm circumference was significantly greater after axillary clearance than sampling alone (P=0.005) or sampling and radiotherapy (P=0.04). Radiotherapy to the axilla after node sampling also resulted in a significant reduction in range of shoulder movement.	An RCT with adequate methodology. Analysis of morbidity was by treatment received. Time-dependent variables presented as Kaplan-Meier curves, log-rank test for statistical differences between the groups.
Tasmuth, 1996 <sup>6</sup> Finland Grade IV	To assess how pain, oedema of the ipsilateral arm, and other symptoms develop during the first year after breast conserving therapy and modified radical mastectomy.	93 women with unilateral non-metastasised breast cancer. (12/105 consecutive women were not included in the final analysis, reasons given).  Median age was 57 to 59 (range 29 to 86).	53/93 women had breast conserving surgery, 40 had modified radical mastectomy, all had axillary clearance.  Surgery was performed by 5 different surgeons.	Pain (subjective), neurological symptoms, oedema of the ipsilateral arm (subjective, or objective i.e. arm circumference at least 2cm more than the preoperative measurement), anxiety (State and Trait Anxiety Inventory) and depression (using a simplified scale developed in Finland).  Assessments were done the day before surgery, and at 1, 6 and 12 months after surgery.	1 year after surgery 19/93 (20%) women subjectively reported lymphoedema in their ipsilateral arm, although subjective measurement of change in arm circumference showed lymphoedema in 38%. Arm lymphoedema was observed more commonly in the mastectomy group.  Statistical analysis revealed no significant correlation between the number of symptoms measured in the ipsilateral arm (sensory disturbance, grip strength, muscle weakness) and any measured levels of anxiety or depression.	Prospective consecutive series, 1993 to 1994.

<p>Tobin, 1993<sup>5</sup> UK Grade V</p>	<p>To evaluate the psychological morbidity of breast cancer-related arm swelling.</p>	<p>50 women with arm lymphoedema related to breast cancer treatment and 50 matched controls who had similar treatment but no arm swelling.</p> <p>Mean age was 56.7 years. Mean duration since treatment was 77 to 80 months. Mean duration of lymphoedema was 49.8 months (SE 0.3).</p> <p>Lymphoedema was defined as a difference of &gt;200ml in arm volume, present for at least 12 months.</p>	<p>psychological morbidity was assessed using various scales .</p>	<p>Functional impairment, assessed using a modified Karnofsky performance scale. Psychiatric morbidity, assessed using a standardised psychiatric interview (Clinical Interview Schedule), the Hospital Anxiety Depression Scale, and the Social Stress and Support Inventory. Psychosocial adjustment, assessed using the Psychosocial Adjustment to Illness Scale.</p>	<p>23/50 women with arm lymphoedema had some functional impairment whereas all of the control group showed absence of impairment (modified Karnofsky performance scale).</p> <p>A standardised psychiatric interview showed greater psychiatric morbidity among women with lymphoedema, especially in areas of anxiety and morbidity, but this was not confirmed by the Hospital Anxiety Depression Scale. No difference was shown between the groups in the patients' own perception of stress (Social Stress and Support Inventory).</p> <p>Women with lymphoedema had significantly poorer overall psychosocial adjustment to their illness (Psychosocial Adjustment to Illness Scale). When broken down in to its component parts the measurement tool showed significant negative effects on vocation (work, school, and home), domestic and social environment (P&lt;0.001), and sexual relations (P&lt;0.01), and psychological distress (P&lt;0.05), but not in extended family relations.</p>	<p>A small matched case-control study reported to be the first controlled study of psychological morbidity associated with breast cancer-related arm swelling. Conducted at The Royal Marsden (1990 to 1991).</p>
<p>Velanovich, 1999<sup>4</sup> USA Grade VI</p>	<p>To define the incidence of postoperative lymphoedema in breast cancer patients and its effect on quality of life.</p>	<p>Incidence: hospital registry data (1990 to 1996) on all patients who underwent axillary node dissection in the management of breast cancer.</p> <p>Quality of life: 101 consecutive patients in one practice who underwent breast surgery.</p>	<p>Assessment of quality of life using a generic quality of life questionnaire (SF-36) applied 6 months to 4 years after surgery.</p>	<p>Incidence of lymphoedema and quality of life.</p>	<p>Incidence: 68/827 (8.3%) patients who underwent axillary lymph node dissection as part of their treatment developed lymphoedema.</p> <p>Patients who developed lymphoedema had significantly lower scores in the domains of role-emotional and bodily pain, compared to those who did not develop lymphoedema. Significantly more patients with lymphoedema, compared to those without lymphoedema, fell below the national norm for bodily pain, mental health and general health.</p>	<p>Prospectively collected registry data and a consecutive patient sample.</p>



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# Management of Advanced, Recurrent, and Metastatic Disease

## 1. Hormone Therapy

### The Questions

- a. Is there evidence from randomised trials that aromatase inhibitors or progestins are better than tamoxifen for first line treatment of metastatic breast cancer in terms of survival and quality of life?
  - Tamoxifen versus anastrozole or letrozole
  - Tamoxifen versus exemestane or formestane
  - Tamoxifen versus megestrol acetate or medroxyprogesterone acetate
- b. Is there evidence from randomised trials that aromatase inhibitors are safe and effective for second line treatment of hormone-dependent (ER+) metastatic breast cancer in post-menopausal women failing tamoxifen therapy?
- c. Is there evidence that routine combined measurement of oestrogen and progesterone receptor status influences decisions about endocrine therapy, and improves outcomes in metastatic breast cancer (ER+ and ER-)?

### Nature of the Research Evidence

- a. Three systematic reviews were identified that summarised largely the same RCTs (Grade D).<sup>1-4</sup> The review by Fossati *et al* was conducted by the Italian Cochrane Centre and is comprehensive.<sup>3</sup> All of the trials included in the later review by Stockler *et al* (co-authors had affiliations with the Cochrane Breast Cancer Group),<sup>1</sup> were included in the earlier Fossati review and there were no additional trials. The question pertinent to this Guidance concerns first line treatment, however, the published systematic reviews had a broader scope. The Fossati review did not separate trials according to first, second or other-line therapy, and only stated percentages of first line treatment patients for the broad comparisons of ‘tamoxifen versus other hormonal therapy’ and ‘tamoxifen plus other hormonal therapy versus tamoxifen alone’. The Stockler review did specify the sub-questions of initial treatment comparing multiple versus single endocrine therapy, and antioestrogens, progestin or aromatase inhibitors versus any other endocrine therapy – consequently this review separates the first line therapy trials. The French review by Leriche *et al* included only two additional small RCTs, one reporting preliminary results and one using high dose medroxyprogesterone acetate.<sup>4</sup> The relevant trials data from these reviews are

summarised in Table 8a. An additional small Japanese trial that compared medroxyprogesterone acetate with tamoxifen in women with advanced or recurrent disease was also identified (Grade II, study not tabulated).<sup>5</sup>

More recently results from an RCT of letrozole versus tamoxifen as first line therapy in postmenopausal women with advanced breast cancer have been published (Table 8b).<sup>6</sup> A combined analysis of two RCTs of anastrozole versus tamoxifen as first line therapy in postmenopausal women, conducted by the Arimidex Study Group, has been reported in abstract only (not tabulated),<sup>7,8</sup> (both trials have also been published separately<sup>9-11</sup>). Data are also published in abstract (not tabulated) from a randomised phase II EORTC study of first line exemestane versus tamoxifen in postmenopausal women with metastatic breast cancer.<sup>12</sup> (All Grade II.)

- b. No systematic review was identified.

The Arimidex Study Group has published a combined analysis of data from two mature multicentre RCTs of anastrozole versus megestrol acetate in postmenopausal women with advanced breast cancer whose disease had progressed after treatment with tamoxifen (Grade II, Table 8b).<sup>13</sup>

Letrozole was compared with megestrol acetate in an RCT in women with advanced breast cancer previously treated with antioestrogens,<sup>14</sup> (Grade II, Table 8b).

(Fadrozole and vorozole are not included in this review.)

A multinational multicentre RCT compared formestane with megestrol acetate as second line therapy in postmenopausal women with advanced breast cancer previously treated with tamoxifen (this trial was supported by Novartis).<sup>15</sup> The Swiss Group for Clinical Cancer Research (SAKK) compared the same second-line treatment regimens in an RCT in postmenopausal women after failure of tamoxifen. Efficacy and toxicity<sup>16</sup> and quality of life<sup>17</sup> were reported (Grade II, Table 8b).

The Exemestane Study Group has reported a multicentre RCT of exemestane versus megestrol acetate in postmenopausal women with advanced breast cancer who experienced failure of tamoxifen (Grade II, Table 8b).<sup>18</sup>

- c. No systematic review was identified. A systematic search failed to identify any primary studies of routine measurement of combined ER and PR status in relation to hormone therapy decisions in patients with metastatic disease.

A prospective study by the Southwest Oncology Group investigated the prognostic significance of PR levels in patients with ER-positive metastatic breast cancer who were treated with tamoxifen,<sup>19</sup> (Grade VI). This study is summarised in Table 8b.

The EORTC Receptor and Biomarker Study Group have evaluated ER and PR receptor assays in quality assessment studies.<sup>20</sup> The UK national external quality assessment scheme for immunochemistry (UK NEQAS-ICC) has been established to minimise the variability between laboratories when assaying ER and PR by immunohistochemistry.<sup>21</sup>

## Summary of the Research Evidence

- a. The evidence from RCTs published up to 1996, as included in published systematic reviews, did not show superiority of aromatase inhibitors or progestins over tamoxifen for survival in metastatic breast cancer in general, or in the smaller group of trials of initial (first line) therapy (Grade I, Table 8a).<sup>1-3</sup> Few trials assessed quality of life. There is some evidence that compared to tamoxifen, other hormonal therapies lead globally to a higher incidence of adverse effects, and a lower incidence of flushing, however, these data were not presented separately for aromatase inhibitors and progestins.<sup>3</sup> The small Japanese trial (n=52) showed no difference between tamoxifen and medroxyprogesterone acetate or alternate combinations of both, in response rate or adverse effects, overall or in women who had not received previous therapy,<sup>5</sup> (Grade II).

More recent RCT data have shown first line therapy with letrozole to be significantly better than tamoxifen for time to progression (HR 0.70, 95% CI 0.60 to 0.82; P=0.0001), time to treatment failure (HR 0.71, 95% CI 0.61 to 0.82; P=0.0001) and overall response rate (OR 1.71, 95% CI 1.26 to 2.31; P=0.0006) in postmenopausal women (n=907) with advanced breast cancer. No difference was shown in the duration of overall response or clinical benefit (i.e. overall response or no change for at least 24 weeks). Survival data were not reported (the median duration of the study was 18 months). No difference was found in adverse events, but each event was counted only once per patient even if it occurred multiple times, which perhaps does not reflect fully patient experience.<sup>6</sup> (Grade II)

A published short article on a multicentre RCT reported a similar time to progression and achievement of complete or partial response in postmenopausal women treated with first line anastrozole (n=340) or tamoxifen (n=328) for advanced breast cancer after 19 months follow-up.<sup>9</sup> A combined analysis of this and another identical multicentre trial (Arimidex Study Group) has shown anastrozole to be at least as effective as tamoxifen with fewer thrombotic events and a lower incidence of vaginal bleeding (abstract only).<sup>7,8</sup>

Results from a randomised phase II EORTC trial (abstract only) showed an overall response rate of 44.6% (25/56) with exemestane and 14.3% (8/56) with tamoxifen. Disease stabilization for six months or more was achieved in 10.7% (6/56) and 25% (14/56), respectively. A similar number of patients in each group experienced dyspnoea (difficulty breathing), fatigue and pain; oedema affected fewer exemestane patients (2/60) than tamoxifen patients (10/57), as did hot flushes (3/60 versus 13/57). One exemestane patient experienced a non-fatal pulmonary embolism. This study will be extended to a phase III RCT with time to progression as the primary outcome.<sup>12</sup>

Overall, the available evidence on survival from randomised trials comes from the earlier trials (published up to 1996) reported in the published systematic reviews, which have not shown first line treatment with an aromatase inhibitor (anastrozole, letrozole, exemestane or formestane) or progestin (megestrol acetate or medroxyprogesterone acetate) to be superior to tamoxifen. The primary endpoint of more recent trials has been time to progression. One RCT of letrozole has shown this drug to be superior to tamoxifen in this respect, whereas two trials of anastrozole have shown that drug to be similar to

tamoxifen. Recording and reporting of adverse effects is inconsistent across trials. A comprehensive review of safety data would have to go beyond what is currently available from RCTs, and is beyond the scope of this review. Quality of life has not been addressed adequately in randomised trials.

- b. Two multicentre RCTs were analysed together by the Arimidex Study Group (Table 8b). A survival benefit was shown with 1mg/d anastrozole compared to megestrol acetate that just reached statistical significance (HR 0.78, 97.5% CI 0.6 to 1.0; P=0.025) based on 516 women, but 10mg/d anastrozole (n=501) showed no significant difference (HR 0.83, 97.5% CI 0.64 to 1.1, P=0.09). The two-year survival rate was higher with either dose of anastrozole compared with megestrol acetate (Grade II). In the megestrol acetate group two women died of causes attributed to adverse drug reactions (stroke and pulmonary embolism) and treatment was withdrawn because of adverse drug reactions from 10/253 patients. No adverse drug reaction deaths were recorded in the anastrozole treated groups but treatment was withdrawn from 5/262 who received 1mg/d anastrozole and 7/246 who received 10mg/d anastrozole because of adverse effects.<sup>13</sup> (Grade II)

The RCT of letrozole versus megestrol acetate showed a higher overall objective tumour response rate with letrozole (2.5mg/d) compared to megestrol acetate (OR 1.82, 95% CI 1.02 to 3.25, P=0.04) or letrozole 0.5mg/d (P=0.004). No difference was shown in time to progression between letrozole 2.5mg/d and megestrol acetate. Time to treatment failure was just statistically significantly longer with letrozole 2.5mg/d than megestrol acetate (RR 0.77, 95% CI 0.61 to 0.99, P=0.04). The median was 5.1 months compared to 3.9 months. Serious adverse experiences (death, life threatening, hospitalisation) were recorded for 29% of women in the megestrol acetate group compared to 10% in the 2.5mg/d letrozole group (95% CI for the difference 11 to 27%). More women discontinued megestrol acetate (11%) than letrozole 2.5mg (3%) because of poor tolerability.<sup>8, 14</sup> (Grade II)

A multicentre RCT that compared formestane with megestrol acetate in 547 women did not show any significant difference in clinical outcome (time to failure, time to progression, overall survival, response rate) or adverse effects.<sup>15</sup> The Swiss Group for Clinical Cancer Research (SAKK) trial compared the same treatment regimens and showed no significant difference in time to treatment failure or response rate. Toxicity was similar with both treatments, except that there were significantly more moderate and severe life threatening cardiovascular events with megestrol acetate (12/81) compared to formestane (3/90; P=0.013).<sup>16</sup> In quality of life as a secondary endpoint, no significant difference was found between treatments.<sup>17</sup> (Grade II)

A multicentre RCT of exemestane versus megestrol acetate showed no significant difference in overall objective response rate (the primary outcome), time to or duration of objective response, or duration of stable disease. Exemestane was shown to confer a longer duration of overall success (60.1 versus 49.1 weeks, P=0.025), and time to tumour progression (20.3 versus 16.6 weeks, P=0.037) and time to treatment failure (16.3 versus 15.7 weeks, P=0.042). Exemestane was associated with similar or marginally improved pain scores, tumour related signs and symptoms, and quality of life parameters. Both drugs were well tolerated.<sup>18</sup> (Grade II)

In summary, the so-called third-generation aromatase inhibitors tested in second-line therapy trials appear to be safer than megestrol acetate, probably have a better effect on quality of life, and are at least as effective clinically as standard treatment with megestrol acetate.

- c. Research evidence specific to routine measurement of combined ER/PR status in relation to hormone therapy decisions and patient outcome in metastatic disease is lacking. It is believed that discrimination between hormone sensitive and insensitive breast cancer could be improved by demonstrating an index of receptor functionality such as the progesterone receptor (PR), which is an oestrogen regulated protein.<sup>20</sup> It is well known that ER or PR can change from positive to negative between a primary and secondary tumour, and there is some evidence that the secondary tumour status is stable with progression to a metastatic site.<sup>22</sup> (Grade VI)

A prospective study in the USA concluded that knowledge of PR levels can improve the pretreatment assessment of women with ER-positive metastatic disease. Higher PR levels significantly and independently correlated with an increased rate of response to tamoxifen treatment, a longer time to treatment failure, and longer overall survival. Knowledge of ER and PR receptor levels, menopausal status and other clinical information, may be a significant predictor of response to tamoxifen treatment.<sup>19</sup> (Grade VI)

A working protocol and scoring system for immunohistochemical detection of ER and PR in breast cancer in the UK has been suggested, although appropriate cut-off values for adjuvant treatment using steroid receptor determination by immunohistochemistry have yet to be determined.<sup>21</sup> The UK national external quality assessment scheme for immunocytochemistry (UK NEQAS-ICC) has been established to minimise the variability<sup>23</sup> between laboratories when assaying ER and PR status using immunohistochemistry.<sup>21</sup> The UK NEQAS-ICC centre's routine immunohistochemical assay for ER and PR has been shown to be 90 to 100% efficient in achieving optimal demonstration of receptor status in breast tumours from over 150 different laboratories.<sup>24</sup>

## 2. Immunotherapy

### The Questions

- a. Is there evidence that determining HER-2/neu (c-erb-B2) receptor status can improve patient outcome in advanced breast cancer?
- b. Is there a reliable test for HER-2/neu (c-erb-B2) receptor status in advanced breast cancer?

### Nature of the Research evidence

- a. The Cancer Care Ontario Practice Guidelines Initiative has conducted a systematic review of the role of Herceptin® (trastuzumab) in the treatment of women with HER2/neu-overexpressing metastatic breast cancer (Grade I/III, Table 8a).<sup>25</sup> NICE has also commissioned a systematic review of the effectiveness of trastuzumab to inform practice guidelines (the review and guidelines are not yet published).

- b. The Cancer Care Ontario Practice Guidelines Initiative systematic review (as above) also addressed the question of the most effective methods of assessing HER2/neu status,<sup>25</sup> (Grade VII).

A recently published consensus statement gives recommendations on HER2/neu status testing in the UK.<sup>26</sup>

## Summary of the Research Evidence

- a. The Canadian systematic review (Table 8a) looked at single agent trastuzumab in one RCT (n=112) that compared standard versus high dose trastuzumab as primary therapy (Table 8a).<sup>25</sup> The overall response rate was 25% (95% CI 14.3 to 36.5) and 27% (15.5 to 39.0) respectively. The median time to progression with standard dose treatment was 3.5 months and the overall average survival was 22.9 months (3.8 and 25.8 respectively in the high dose group). Two uncontrolled Phase II trials in women who had prior chemotherapy for metastatic disease were also described. The larger study (n=213) reported a total response rate of 15% (95% CI 11 to 21), a median duration of response of 9.1 months, and a median overall survival of 13 months. The smaller study (n=43) reported an 11.6% overall response rate (95% CI 4.5 to 26) and median time to progression 5.1 months. The larger Phase II study observed improved scores for global quality of life and social functioning (EORTC-QLQ-30) after 12 weeks of treatment, but no change in physical or role functioning or fatigue (Grade I/III).

Trastuzumab in combination with chemotherapy was assessed in one multicentre RCT and in two uncontrolled Phase II studies. The RCT reported a significantly longer time to disease progression (7.2 versus 4.5 months,  $P<0.0001$ ), higher overall response rate (45% versus 29%,  $P<0.001$ ), and greater 1-year survival (79% versus 68%,  $P<0.01$ ) with trastuzumab plus chemotherapy versus chemotherapy alone in women who had not previously had chemotherapy for metastatic disease (n=469). No significant difference was shown in quality of life. A small Phase II study (n=37) of trastuzumab and cisplatin in previously treated women reported complete or partial response in seven women (24%) and a median time to progression of 5.3 months. An ongoing Phase II study of trastuzumab and paclitaxel in previously treated women has reported an overall response rate of 64% (20/28 HER2/neu positive women and 3/8 HER2/neu negative women).

The incidence of cardiac dysfunction was reported in the Canadian review to be between 3 and 13% in uncontrolled studies, and 21% (50/234) among women who received trastuzumab in the multicentre RCT of trastuzumab with and without chemotherapy (the incidence among women who received chemotherapy alone was 4.8% (11/230). Risk may be increased with concomitant anthracyclines as in the latter RCT the incidence among women who received combination therapy with adriamycin/cyclophosphamide plus trastuzumab was 40/143 (28%) compared to 10/91 (11%) who received paclitaxel plus trastuzumab (Grade I/III).

There is some evidence from the multicentre RCT of trastuzumab with chemotherapy, and the largest phase II trastuzumab single-agent efficacy trial, to suggest that beneficial effects are largely limited to patients with the highest level of protein over-expression (measured on a scale of 0 to 3+). In the RCT,

the response rate to trastuzumab plus paclitaxel in 3+ tumours was 30/68 (44%) compared to 5/24 (21%) for 2+ tumours, and to trastuzumab plus adriamycin/cyclophosphamide in 3+ tumours it was 57/108 (53%) compared to 14/35 (40%) in 2+ tumours. In the uncontrolled phase II study the response rate to trastuzumab was 29/172 (17%) for 3+ tumours and 2/50 (4%) in 2+ tumours.

The Canadian review has identified five additional ongoing trials related to the use of trastuzumab in metastatic breast cancer (randomised and/or phase II) from which data are not yet available.

The NICE review and guidelines on trastuzumab are not yet published.

- b. A systematic review (Table 8a) assessed data from 16 case series that examined methods of assessment of HER2/neu status (3 additional reports are also under review by the authors). It concluded that newer molecular techniques for measuring HER2/neu DNA amplification (FISH, PCR) are accurate and reliable in paraffin embedded tumour samples. Also that there is good correlation between DNA amplification and protein over-expression. Measurement of protein over-expression by immunohistochemistry has been widely used to assess HER2/neu status clinically. However, due to numerous technical issues associated with the validity and predictive value of immunohistochemistry testing, further validation studies are needed to determine the most reliable method,<sup>25</sup> (Grade III).

A consensus statement from UK specialist groups recommends immunohistochemistry to determine HER2/neu status, with FISH (fluorescent in situ hybridisation) as a follow-up test for ambiguous results (GradeVII). Three HER2/neu testing laboratories have been established in London, Nottingham and Glasgow, and these run an interlaboratory quality assurance scheme.<sup>26</sup> The authors of the Canadian review state that a prospective study of patients receiving trastuzumab should be carried out to explore the relationship of over expression measured by IHC with that determined by a DNA method (FISH or PCR).<sup>25</sup>

### 3. Bone Metastases

#### The Questions

- a. What is the role of bisphosphonates in the management of bone metastases, and for the prevention of bone metastases in the primary and adjuvant setting?
- b. Do multidisciplinary teams for breast cancer need additional skills to manage bone metastases?
- c. What service structure is required to ensure adequate management of spinal cord compression as a surgical oncological emergency (from diagnosis by a physician to emergency access to surgery) to improve patient outcome in terms of mobility and function?

#### The Nature of the Research Evidence

- a. A systematic review of RCTs (Grade D) has been conducted on the use of bisphosphonates in breast cancer patients, for treatment or prevention of bone



metastases, and management of bone pain. The original report was published in 1998, and the most recent update in May 2001.<sup>27</sup> The review is summarised in Table 8a.

There are several on-going trials, including placebo controlled comparisons with oral pamidronate (EORTC-10924), etidronate (UAB-248 NCI-V83-0029 and UCCRC-3552 NCI-V83-0138), and ibandronate (MF-4434).

- b. No research evidence was identified. The British Association of Surgical Oncology (BASO) has published guidelines for the management of metastatic bone disease, including the composition of the breast care team,<sup>28</sup> (Grade VII).
- c. BASO Guidelines (as above).<sup>28</sup>

## Summary of the Research Evidence

- a. The systematic review is summarised in Table 8a. (Several new trials are still under review by the authors.)<sup>27</sup>

Meta-analysis of six RCTs (n=1155) of the bisphosphonates pamidronate or clodronate versus placebo or observation, in patients with bone metastases from breast cancer, showed a significant reduction in pathological fractures with bisphosphonates (overall risk ratio 0.72, 95%CI 0.6 to 0.87). Meta-analysis of five RCTs (n=1122) showed a significant reduction in the need for radiotherapy for bone pain with bisphosphonates (overall risk ratio 0.61, 95%CI 0.51 to 0.73). Four small RCTs provided evidence to support the use of bisphosphonates as part of a pain management programme in a variety of different cancers including breast cancer. Five RCTs measured some aspect of quality of life and three of them reported some benefit with bisphosphonate treatment. Six RCTs showed no survival benefit with clodronate or pamidronate (Grade D). Serious adverse effects appear to be uncommon although rare ocular complications with pamidronate have been documented that require urgent referral to an ophthalmologist. When to start and when to stop treatment with bisphosphonates is not yet well defined (R. Coleman, personal communication).<sup>29</sup>

For prevention of bone metastases or related skeletal events, in women with breast cancer without bone metastases, the evidence from four RCTs (n=1638) is not strong or consistent.<sup>27</sup> There might be some delay in bone metastasis development with clodronate, but no effect on overall disease-free survival or overall survival (Grade D). The relevant trials are only just beginning and will not report for five years or more. The use of bisphosphonates in the adjuvant setting should, therefore, be confined to the treatment and prevention of osteoporosis, which falls within their existing licence (R. Coleman, personal communication). An RCT in 148 premenopausal women with breast cancer without skeletal metastases has shown that chemotherapy induced ovarian failure causes rapid bone loss which can be significantly reduced by oral clodronate (study not tabulated).<sup>30</sup>

- b. No research evidence was identified. The British Association of Surgical Oncology Guidelines for the management of metastatic bone disease state that additional personnel on the breast care team should be an orthopaedic surgeon and a radiologist with an interest in metastatic breast cancer. This is based on

consensus expert opinion in the absence of directly applicable clinical studies of good quality,<sup>28</sup> (Grade VII). As well as liaison with an orthopaedic surgeon links between the cancer unit and the centre for spinal surgery need to be in place. Physiotherapy is an important component in the diagnosis of mechanical pain and rehabilitation (R. Coleman, personal communication).

The BASO Guidelines state that the cancer unit should aim to educate GPs in the management of women with skeletal pain and a history of breast cancer. Rapid referral back to the breast team where necessary would avoid delays in diagnosis and appropriate treatment (Grade VII). All changes in diagnosis and management should be communicated promptly back to the GP. The Guidelines state that one surgeon within the trauma team should be identified as the lead clinician with responsibility for metastatic bone disease.<sup>28</sup>

- c. Research evidence is lacking. Current recommendations are based on consensus expert opinion (Grade VII) and rigorous audit of results is recommended.<sup>28</sup> Spinal cord compression is an oncological emergency and patients should be referred as an emergency to the cancer centre for combined surgical, oncological and radiological assessment. Spinal surgery services, emergency access to MRI (including weekends) and emergency radiotherapy services (again at weekends) are essential. A spinal team should be defined and accessible for emergencies (Grade VII).

**Table 8a. Systemic therapy for advanced disease: systematic reviews**

Study, grade	Aims of study	Included studies	Outcome measures	Results	Comments
<b>Hormone therapy</b>					
Fossati, 1998 <sup>3</sup> (Italian Cochrane Centre) Grade I	To summarise RCTs of chemotherapy, endocrine therapy and chemotherapy plus endocrine therapy for metastatic breast cancer.	<p>RCTs (published between 1980 and 1996), that compared:</p> <p>Aromatase inhibitors versus tamoxifen (4 RCTs),</p> <p>Megestrol acetate (MA) versus tamoxifen (6 RCTs),</p> <p>Medroxyprogesterone acetate (MPA) versus tamoxifen (5 RCTs),</p> <p>Tamoxifen + MA versus tamoxifen alone (2 RCTs),</p> <p>Tamoxifen + MPA versus tamoxifen alone (3 RCTs).</p> <p>Not all patients had the assigned therapy as first line treatment. Percentages are reported only for the broad comparisons of tamoxifen versus other hormonal therapy (62% of 5160 patients in 35 RCTs), and tamoxifen plus other hormonal therapy versus tamoxifen alone (52% of 2949 patients in 22 RCTs).</p>	Survival, response rate, adverse effects, quality of life.	<p>Meta-analysis of 4 RCTs (n=954) of aromatase inhibitors versus tamoxifen gave a hazard ratio of death, HR 0.94 (95%CI 0.80 to 1.10).</p> <p>Meta-analysis of 6 RCTs (n=708) of MA versus tamoxifen gave HR 1.09 (95%CI 0.91 to 1.30).</p> <p>Meta-analysis of 5 RCTs (n=531) of MPA versus tamoxifen gave HR 0.97 (95%CI 0.79 to 1.20).</p> <p>Meta-analysis of 2 RCTs (n=375) of tamoxifen + MA versus tamoxifen alone gave HR 0.73 (95%CI 0.57 to 0.93).</p> <p>Meta-analysis of 3 RCTs (n=290) of tamoxifen + MPA versus tamoxifen alone gave HR 0.98 (95%CI 0.69 to 1.38).</p> <p>Compared to tamoxifen, other hormonal therapies lead globally to a higher incidence of fatigue/lethargy, congestive heart failure, alopecia, oedema, rash and weight gain, and a lower incidence of flushing.</p> <p>There were insufficient data on quality of life.</p>	<p>Clear review methodology, although the included RCTs were not assessed for quality. Reporting of individual study details was limited due to the large scope of the review.</p> <p>Survival data were available from relatively few relevant trials identified.</p>
Leriche, 1997 <sup>1</sup> Grade I	To investigate the therapeutic efficacy of progestins compared to other hormone therapies for breast cancer with bone metastases.	Includes 3 RCTs of MA versus tamoxifen, and 4 RCTs of MPA versus tamoxifen.	Remission or progression, global response according to standard criteria.	<p>Only the two RCTs not included in the Fossati and Stockler reviews are summarised here.</p> <p>Preliminary results from 1 RCT (n=68) of tamoxifen versus MA showed no difference in efficacy.</p> <p>1 RCT (n=33) of tamoxifen versus high dose MPA showed a significantly higher global response with MPA.</p>	<p>A fair quality review, possible language bias.</p> <p>Includes only two small RCTs (published in 1986 and 1982) that were not included in the Fossati<sup>3</sup> or Stockler<sup>1</sup> reviews.</p>



Study, grade	Aims of study	Included studies	Outcome measures	Results	Comments
Stockler, 2000 <sup>1, 2</sup> Grade I	To summarise the evidence from RCTs of chemotherapy and endocrine therapy in metastatic breast cancer.  The following relevant subgroup questions were addressed:  Initial treatment with multiple versus single endocrine therapy.  Initial treatment with any antiestrogen, progestin or aromatase inhibitor versus any other endocrine therapy.	Only the trials of initial treatment are summarised here (as all trials included in this review were described in the review by Fossati <i>et al.</i> )  3 RCTs of tamoxifen versus MA.  2 RCTs of tamoxifen versus MPA.  1 RCT of tamoxifen versus formestane.  2 RCTs of combination tamoxifen plus MA versus either drug alone.	Survival, quality of life.	Meta-analysis showed no evidence that any one class of endocrine agent was superior to the others in terms of survival, based on 3 RCTs of initial treatment with tamoxifen versus MA (n=309), 2 RCTs of initial treatment with tamoxifen versus MPA (n=311), and 1 RCT of initial treatment with tamoxifen versus formestane (n=409). There were no RCTs of initial treatment with anastrozole or letrozole versus tamoxifen.  None of these trials reported quality of life using validated instruments.	Although the search for trials was limited to one database this review identified the same trials as the Fossati review. <sup>3</sup> Otherwise the review methodology was adequate.
<b>Immunotherapy</b>					
Crump 2001 <sup>25</sup> Grade I/III	To address the questions:  What is the role of trastuzumab in the treatment of women with HER2/neu overexpressing metastatic breast cancer?  What are the most effective methods of assessing HER2/neu status?	<i>Efficacy</i>  Single agent trastuzumab: 1 RCT of two doses in previously untreated metastatic disease; 2 Phase II trials in women who had prior chemotherapy for metastatic disease.  Combination therapy: 1 RCT of the addition of trastuzumab to chemotherapy in women who had not previously had chemotherapy for metastatic disease. 2 Phase II trials with cisplatin or paclitaxel in previously treated women.  <i>Testing</i>  16 case series (3 additional reports are under review).	<i>Efficacy</i>  Complete, partial and overall response rates, duration of response, survival, and toxicity.  <i>Testing</i>  Concordance between DNA testing (FISH, PCR) methods and protein over expression (IHC).	<i>Single agent trastuzumab</i>  An uncontrolled Phase II study (n=43) reported an overall response rate of 11.6% (95% CI 4.5 to 26) and a median time to progression of 5.1 months. Another Phase II study (n=213) reported a total response rate of 15% (95% CI 11 to 21). The median duration of response was 9.1 months and the median overall survival 13 months. Improved scores for global quality of life and social functioning (EORTC-QLQ-30) was observed after 12 weeks of treatment, but no change in physical or role functioning or fatigue.  A randomised comparison of standard versus high dose trastuzumab as primary therapy (n=112) reported similar overall response rates, 25% in the standard dose group (95% CI 14.3 to 36.5) and 27% (15.5 to 39.0) with the high dose. Median times to progression with standard dose treatment was 3.5 months and overall average survival 22.9 months (3.8 and 25.8 respectively in the high dose group).  <i>Trastuzumab in combination with chemotherapy</i>  A multicentre RCT (n=469) reported a significantly longer time to disease progression (7.2 versus 4.5 months, P<0.0001), higher overall response rate (45% versus 29%, P<0.001), and greater 1-year survival (79% versus 68%, P<0.01) with trastuzumab plus chemotherapy versus chemotherapy alone. No significant difference was shown in quality of life (no data reported).	7 additional phase II trials are currently under review by the authors. An additional 5 ongoing trials have been identified from which data are not yet available.  Language bias is a possibility in this review.

Study, grade	Aims of study	Included studies	Outcome measures	Results	Comments
				<p>An uncontrolled Phase II study (n=37) of trastuzumab and cisplatin reported complete or partial response in 7 women (24%) and median time to progression 5.3 months. An ongoing Phase II study of trastuzumab and paclitaxel has reported an overall response rate of 64% (20/28 HER2/neu positive and 3/8 HER2/neu negative).</p> <p>The incidence of cardiac dysfunction in uncontrolled studies is 3 to 13% (2 deaths have been reported), and was 21% among women who received trastuzumab in the RCT of trastuzumab with and without chemotherapy (above). Risk may be increased with concomitant anthracyclines.</p> <p><i>Testing</i></p> <p>Molecular techniques for measuring HER2/neu DNA amplification (FISH, PCR) are accurate and reliable in paraffin embedded tumour samples, correlation between DNA amplification and protein over expression (immunohistochemistry) is good. Further studies of the validity and predictive value of immunohistochemistry are needed.</p>	
<b>Bone metastases</b>					
<p>Bloomfield 2001<sup>27</sup></p> <p>Grade I</p>	<p>To review evidence from RCTs on whether bisphosphonates should be used in patients with bone metastases from breast cancer, and on bisphosphonates for the prevention of bone metastases in patients with breast cancer.</p>	<p>Treatment: 7 RCTs of clodronate or pamidronate versus placebo or observation, in women with bone metastases from breast cancer.</p> <p>Management of bone pain: 4 RCTs of clodronate or pamidronate versus placebo, in patients with breast, lung, prostate cancer or myeloma (65% had breast cancer).</p> <p>Prevention: 4 RCTs of clodronate or pamidronate versus placebo or observation, in women with breast cancer without bone metastases.</p>	<p>Primary outcome measures were reduction in skeletal events (excluding hypercalcaemia), reduction in bone pain, and pain.</p> <p>Secondary outcome measures were the need for radiotherapy, quality of life, adverse effects and survival.</p>	<p>Pathological fractures: meta-analysis of 6 RCTs (n=1155) showed a significant reduction with bisphosphonates, overall risk ratio 0.72, 95% CI 0.6 to 0.87, P=0.0006 (no significant heterogeneity between trials).</p> <p>Need for radiotherapy for bone pain: meta-analysis of 5 RCTs (n=1122) showed a significant reduction with bisphosphonates, overall risk ratio 0.61, 95% CI 0.51 to 0.73, P&lt;0.00001 (no significant heterogeneity between trials).</p> <p>Management of bone pain: 2 RCTs (n=135) of oral clodronate showed little difference in pain control compared to placebo. A cross-over RCT (n=21) of intravenous clodronate showed no significant difference in patient preference compared to placebo, although pain scores were significantly lower with clodronate. One RCT (n=52) showed a non-significant trend towards better pain control with intravenous pamidronate compared to placebo.</p> <p>Prevention: 4 RCTs (n=1638) did not provide strong or consistent evidence that bisphosphonates reduce the occurrence of bone metastases or skeletal events.</p> <p>5 RCTs measured aspects of quality of life, 3 reported some benefit.</p> <p>6 RCTs (n=1416) showed no overall survival benefit with bisphosphonates.</p> <p>Of 18 RCTs (n=3488), none has reported major adverse events, although case reports do exist of rare serious ocular complications with pamidronate.</p>	<p>A thorough review regularly updated. New trials are currently under review by the authors.</p>



**Table 8b. Systemic therapy for advanced disease: primary studies**

Study, country, grade	Aims of study	Participants	Intervention	Outcome measures	Results	Comments
<b>Hormone therapy</b>						
Buzdar, 1998 <sup>13</sup> International, multicentre trial Grade II	A prospective survival analysis of combined data from two RCTs of anastrozole versus megestrol acetate in postmenopausal women with advanced breast cancer whose disease had progressed after treatment with tamoxifen.	764 postmenopausal women whose disease had progressed after treatment with tamoxifen. Mean age 65 to 66 (+/- SD 9.9 to 10.9).  Exclusion criteria: ER- (except those who had a previous treatment response to tamoxifen), >1 previous cytotoxic or endocrine therapy for advanced disease, concurrent illness or abnormality that would compromise safety or interpretation.	Anastrozole (1mg and 10mg/d) versus megestrol acetate (40mg four times a day).	Time to progression was the primary endpoint.  This is a report of a prospectively planned survival analysis. An analysis of tolerability data is also presented.  Median follow-up 31.2 months for survival data; 12 months for tolerability.	1mg/d anastrozole (n=263) showed a survival benefit that just reached statistical significance compared to megestrol acetate (n=253) HR 0.78, 97.5% CI 0.6 to 1.0 (P=0.025). 10mg/d anastrozole (n=248) showed a non-significant survival benefit, HR 0.83, 97.5% CI 0.64 to 1.1 (P=0.09) compared to megestrol acetate. The two-year survival rate was 56.1% in the 1mg/d anastrozole group, 54.6% in the 10mg/d anastrozole group, and 46.3% in the megestrol acetate group.  Treatment was withdrawn because of adverse drug reactions in 10/253 megestrol acetate patients, 5/262 who received 1mg/d anastrozole and 7/246 who received 10mg/d anastrozole. Two deaths from adverse drug reactions occurred in the MA group (one stroke, one pulmonary embolism), none in either anastrozole group. Anastrozole was more often associated with transient diarrhoea.	An RCT. Anastrozole doses double-blind, MA open-label. Allocation concealment not reported. Analysis was adjusted for multiple treatment comparisons, P<0.025 is statistically significant.

Study, country, grade	Aims of study	Participants	Intervention	Outcome measures	Results	Comments
<p>Dombrowsky, 1998<sup>14</sup></p> <p>International, multicentre trial</p> <p>Grade II</p>	<p>To compare letrozole and megestrol acetate as second line treatment in postmenopausal women with advanced breast cancer previously treated with antioestrogens.</p>	<p>551 postmenopausal women with locally advanced, locoregionally recurrent, or metastatic breast cancer previously treated with antioestrogens. ER/PR status positive or unknown.</p> <p>Exclusion criteria included rapidly progressive disease, previous first line endocrine therapy other than antioestrogens for advanced disease, history of DVT or pulmonary embolism, and uncontrolled cardiac disease.</p>	<p>Letrozole (2.5mg or 0.5mg/d) versus megestrol acetate (160mg/d).</p>	<p>The primary outcome was overall objective tumour response (complete response and partial response). Other outcomes were time to progression, time to treatment failure, time to death, duration of objective response. Duration of clinical benefit was added later.</p>	<p>The objective tumour response rate of 24% with letrozole 2.5mg (n=174) was significantly higher than the 16% achieved by megestrol acetate (n=189) (odds ratio, OR 1.82, 95% CI 1.02 to 3.25, P=0.04). Letrozole 0.5mg (n=188) was not superior to megestrol acetate (P=0.11).</p> <p>Since the median duration of objective response was not reached in the letrozole 2.5mg group it was concluded that it was significantly longer compared to the megestrol acetate group (risk ratio, RR 0.42, 95% CI 0.20 to 0.86, P=0.02) and the 0.5mg letrozole group.</p> <p>No difference was shown in time to progression between letrozole 2.5mg (5.6 months) and megestrol acetate (5.5 months, RR 0.8, 95% CI 0.62 to 1.02, P=0.07).</p> <p>Time to treatment failure was longer in the letrozole 2.5mg group compared to megestrol acetate (RR 0.77, 95% CI 0.61 to 0.99, P=0.04). Median 5.1 months compared to 3.9 months, respectively.</p> <p>No difference was shown in overall survival between letrozole 2.5mg (or 0.5mg) and megestrol acetate (RR 0.82, 95% CI 0.63 to 1.08, P=0.15).</p> <p>Adverse experiences were recorded up to 33 months follow-up and are reported only as %. 85% of women who received letrozole 2.5mg/d reported adverse experiences compared to 90% who received megestrol acetate, and 78% who received letrozole 0.5mg/d. Serious adverse experiences (death, life threatening, hospitalisation) were more common in the megestrol acetate group (29%) than with letrozole 2.5mg (10%, 95% CI for the difference 11 to 27%). More women discontinued megestrol acetate because of poor tolerability (11%) than discontinued letrozole 2.5mg (3%, 95% CI for the difference 2 to 12%).</p>	<p>An RCT. Double-blind. Allocation concealment not reported. Patients who took study medication were analysed, exclusions were not reported. P=0.05 was accepted as statistically significant but not adjusted for multiple comparisons or multiple end points. Core data were analysed at 9 months, the extension data presented here were analysed 6 months later although no interim analysis was planned. The actual significance of reported P values should, therefore, be interpreted with caution.</p>



Study, country, grade	Aims of study	Participants	Intervention	Outcome measures	Results	Comments
Freue, 2000 <sup>15</sup> International, multicentre trial Grade II	To compare the efficacy and safety of formestane and megestrol acetate as second line therapy in postmenopausal women with advanced breast cancer previously treated with tamoxifen.	547 postmenopausal women with advanced breast cancer previously treated with tamoxifen. ER/PR status positive or unknown. Women who had first line endocrine therapy with drugs other than tamoxifen were excluded.	Formestane (250mg every 2 weeks) versus megestrol acetate (160mg/d), for 12 months.  Follow-up was 5 years for survival analysis.	The primary outcome was time to failure; time to progression, overall survival, overall response, and adverse effects were also measured.  Follow-up for 5 years or until death for survival data.	Analysis was by intention-to-treat (formestane 276, megestrol acetate 271). 406 women discontinued treatment prematurely, because of disease progression (formestane 179/276, megestrol acetate 157/271), adverse events (formestane 3, megestrol acetate 13), or other given reasons (formestane 22, megestrol acetate 32).  No clinically relevant difference in time to failure, time to progression, or overall survival was observed. No statistically significant difference in response rate was shown. The findings were similar when only evaluable patients were analysed.  No statistical difference was shown in adverse events related to trial medication, or between the number of women who discontinued treatment prematurely because of adverse events.	An unblinded RCT, allocation concealment not reported.
Kaufmann, 2000 <sup>18</sup> International, multicentre trial Grade II	To determine the antitumour activity and tolerability of exemestane as second line treatment for postmenopausal women with progressive advanced breast cancer after treatment with tamoxifen.	769 postmenopausal women with progressive advanced breast cancer after treatment with tamoxifen. Women were excluded if ER and/or PR negative (except those who had a previous treatment response to tamoxifen), or had prior treatment with a hormonal agent other than tamoxifen. Median age 65 years (range 30 to 91).	Exemestane (25mg/d) versus megestrol acetate 40mg 4-times daily. A double-dummy placebo was used.  The overall median follow up was 48.9 weeks.	The primary endpoint was overall objective response rate (the proportion of patients who achieved complete or partial responses, confirmed by blinded external peer review); other measures of response rate, quality of life, and adverse events were also recorded.  Follow-up until end of treatment.	The difference in overall objective response rate between exemestane and megestrol acetate was not significant (-2.6%, 95% CI -7.5 to +2.3). Time to or duration of objective response, and duration of stable disease were also not significantly different.  Duration of overall success, however, was significantly greater with exemestane (60.1 versus 49.1 weeks, P=0.025), as was time to tumour progression (20.3 versus 16.6 weeks, P=0.037) and time to treatment failure (16.3 versus 15.7 weeks, P=0.042).  Improvements in pain score and tumour related signs and symptoms were similar in both treatment groups. In the quality of life assessment, exemestane patients showed significantly better improvements in physical and role functioning, global health, fatigue, difficulty of breathing, and constipation, whereas megestrol acetate patients had significantly better improvements in emotional function, appetite loss and pain. Other quality of life parameters were similar between the groups.  Both drugs were well tolerated. Weight gain was more common with megestrol acetate.	A double-blind RCT, allocation concealment not reported. A lot of secondary outcomes were analysed.



Study, country, grade	Aims of study	Participants	Intervention	Outcome measures	Results	Comments
Mouridsen, 2001 <sup>6</sup> International, multicentre trial Grade II	To compare the efficacy and tolerability of letrozole and tamoxifen as first line therapy in post-menopausal women with advanced breast cancer.	907 postmenopausal women with locally advanced, locoregionally recurrent or metastatic breast cancer (841/907 women had metastatic disease). ER and/or PR + or receptor status unknown. One prior chemotherapy for advanced disease was allowed if there was evidence of progression within 3 months before enrolment.	Letrozole (2.5mg/d) versus tamoxifen (20mg/d).  Women could crossover (double blind) to the alternative drug after disease progression or discontinuation due to adverse events, at the discretion of the investigators.	The primary outcome was time to progression (including discontinuation of treatment with documented evidence of clinical deterioration or death due to breast cancer). Secondary endpoints were overall objective response rate and duration, rate and duration of clinical benefit, time to treatment failure, overall survival, and tolerability.  Data were analysed when the median duration of the study was 18 months.	The median time to progression was 41 weeks with letrozole and 26 weeks with tamoxifen (HR 0.70, 95% CI 0.60 to 0.82; P=0.0001). Multivariate analysis adjusted for receptor status, prior adjuvant therapy, and the dominant site of disease gave a similar result.  The median time to treatment failure was 40 weeks with letrozole and 25 weeks with tamoxifen (HR 0.71, 95% CI 0.61 to 0.82; P=0.0001).  The overall response rate was higher with letrozole (30%) than with tamoxifen (20%) (OR 1.71, 95% CI 1.26 to 2.31; P=0.0006), but the median duration of overall response was not significantly different (102 versus 100 weeks).  The rate of clinical benefit (overall response or no change for at least 24 weeks) was higher with letrozole (OR 1.55, 95% CI 1.19 to 2.01; P=0.001), but the median duration was not significantly different (81 versus 84 weeks).  Survival data are said to be immature and are not reported.  Overall, 408/455 (90%) women given letrozole suffered an adverse event compared to 394/455 (87%) given tamoxifen. A similar number of women in each group suffered hot flushes, nausea and hair thinning, however, to what extent is not reported as adverse events were counted only once per patient, even if an event occurred multiple times.  These data were analysed at 18 months follow-up. 111 were still receiving letrozole, and 67 tamoxifen. Of 729 women who discontinued their allocated treatment, 197 women had crossed-over to tamoxifen, and 194 to letrozole.	A double-blind RCT, allocation concealment not reported. A power calculation was reported for the primary outcome. The cross-over design was pre-defined in the protocol.  Analysis of adverse events appears less thorough and reporting of it less transparent than the efficacy analysis.
Ravdin, 1992 <sup>19</sup> USA Grade VI	To assess the importance of progesterone receptor (PR) in the prediction of the response of breast cancer patients with advanced disease to endocrine therapy.	A prospective trial (SWOG 8228 ) in women with newly diagnosed metastatic ER+ breast cancer.  Hormone receptor assays were performed in quality control programme laboratories. The study was conducted between 1982 and 1987.	ER and PR levels were determined by ligand-binding assays. Women then received tamoxifen as first endocrine therapy for metastatic disease.	Response to tamoxifen therapy (complete response, partial response or stable disease for more than 6 months), time to treatment failure, and overall survival.	Of the 398 patients entered 342 were eligible and assessable.  Higher PR levels independently correlated with a better response to tamoxifen, longer time to treatment failure and longer overall survival.  The response rate could be as high as 86% for postmenopausal women with ER >38fmol/mg and PR >392fmol/mg, and as low as 24% in premenopausal women (exploratory analysis).	Univariate and multivariate analysis was performed. Patient numbers were small for some multivariate analyses. Seven women whose assays were done at a quality controlled laboratory were not analysed.



Study, country, grade	Aims of study	Participants	Intervention	Outcome measures	Results	Comments
Thurlimann, 1997 <sup>16, 17</sup> Switzerland Grade II	To compare the efficacy and tolerability of formestane with megestrol acetate as second line therapy in postmenopausal women with advanced breast cancer previously treated with tamoxifen.	177 postmenopausal women with advanced breast cancer previously treated with adjuvant or palliative tamoxifen. Women given other endocrine therapy after tamoxifen failure were excluded. Median age 65 years (range 43 to 87). Of 177 women included, 19 were known ER negative and 39 PR negative.	Formestane (250mg every 2 weeks) versus megestrol acetate (160mg/d).	The primary outcomes were time to treatment failure and toxicity (presence of any of the following, 3kg or more weight gain, thromboembolism, hypertension). Quality of life was a secondary endpoint.	No significant difference was shown in time to treatment failure or response rate based on analysis of 173 evaluable patients. Toxicity was similar with both treatments. Moderate and severe life threatening cardiovascular events were significantly more common with megestrol acetate (12/81) compared to formestane (3/90), P=0.013. There was no statistically significant difference shown in quality of life by treatment (n=177; overall 83% of expected quality of life forms were completed).	An unblinded RCT with adequate concealment of allocation. Loss to follow-up 2% per group.  After about 1½ years recruitment the inclusion criteria were changed to allow pre-treatment with one chemotherapy regimen for advanced disease; recruitment continued for another 2½ years.
Vergote, 2000 <sup>9</sup> International, multicentre trial Grade II	To compare the efficacy and tolerability of anastrozole and tamoxifen as first line therapy in postmenopausal women with advanced breast cancer.	668 postmenopausal women with advanced breast cancer (ER+ or unknown receptor status). Age not reported.	Anastrozole (1mg/d) versus tamoxifen (20mg/d).	Time to progression, objective response (achievement of complete or partial response), tolerability. Follow-up was 19 months.	Median time to progression was 8.2 months in the anastrozole group and 8.3 months in the tamoxifen group HR=0.99, no confidence interval given). 33% of women given anastrozole achieved a complete or partial response compared to 32.6% in the tamoxifen group. The incidence of depression, tumour flare, gastrointestinal disorders, hot flushes, vaginal dryness and weight gain was similar (no data given). Thromboembolic events occurred in 4.8% of anastrozole patients versus 7.3% with tamoxifen, and vaginal bleeding occurred in 1.2% of anastrozole patients versus 2.4% with tamoxifen.	A double-blind RCT, allocation concealment not reported. Published as a short report with few details. A combined analysis with another identical trial has been published in abstract (Arimidex study Group). <sup>7</sup>

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## Appendix 1

# Analysis of the Potential Economic Impact of Key Areas of the Guidance Update

Sue Ward and Santiago Gutierrez

School of Health and Related Research,  
University of Sheffield

### Contents for Appendix 1

Summary .....	133
Introduction .....	137
Process and Methods .....	137
Cost Impact Analysis .....	138
Conclusions .....	154
References.....	155

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## Summary

A short exercise has been undertaken to estimate the cost impact of recommendations in the updated guidance. Only the cost impact of significantly different changes from the recommendations in the original guidance were considered. A sub-group of the Editorial Board identified three specific areas:

1. increased use of bisphosphonates for treatment of bone metastases
2. changes in the nature and use of anthracycline-based regimens for adjuvant chemotherapy
3. opportunity cost of long-term follow-up of asymptomatic patients

The cost implications of the update outside these areas have not been considered.

### Cost impact of implementing the guidance in England and Wales

	Cost impact (£m )
Bisphosphonates	17.2
Anthracycline-based regimens	3.8
<b>TOTAL</b>	<b>21.0</b>
Opportunity cost of long-term follow-up	(9.3)

Note: All costs are estimated annual costs

### Use of Bisphosphonates

The guidance update states that:

*“The symptoms of bone metastases may respond to systemic interventions particularly hormone therapy and treatment with bisphosphonates;” and “they should be given for as long as skeletal disease remains an important clinical problem.”*

Bisphosphonates have been shown to be effective in reducing bony complications in patients with metastatic breast cancer. The current cost of treatment for a typical Cancer Network with a population of 1.5 million is estimated at £110,000 per annum. This assumes that only one third of the patients with bone metastases (50% of high priority patients) receive treatment and the average treatment duration is six months. This figure includes both drugs and administration costs. On this assumption, the current cost of treatment in England and Wales is estimated to be around £3.9 million per annum.

The guidance is likely to impact in two areas. Firstly a potential increase in the volume of patients receiving bisphosphonate therapy, given that not all patients who could benefit from these drugs are currently prescribed them. Secondly a potential increase in the duration of therapy.

The central scenario assumes that in the future 100% of high priority patients receive bisphosphonates and the average treatment duration is 15 months. The cost of treatment is therefore predicted to rise by £17.2 million per annum, an increase of 445%.

Assuming that 100% of high priority patients will receive bisphosphonates and the average treatment duration is 18 months, the cost of treatment would be estimated to rise to approximately £25.6 million, an increase of £21.7 million per annum (560%). This figure is likely to be an upper ceiling based on leading clinical opinion of best practice.

Cost savings from the reduction in skeletal-related events (for instance reduction in the number of fractures and the requirement for radiation for bone pain) resulting from the increased use of bisphosphonates, although not known with certainty, are not likely to be trivial. Further research is needed to estimate these cost savings.

### **Use of Anthracycline-based Chemotherapy**

The update recommends that:

*“Women at intermediate or high risk of recurrence, who have not had neo-adjuvant chemotherapy, should normally be offered four to eight cycles of multiple-agent chemotherapy which includes anthracyclines.”*

A survey of UK oncology centres showed that CMF was still used in many centres in 1999. However anthracycline-based regimens are increasingly being used for adjuvant therapy in the UK. Common regimens include FEC (fluorouracil, epirubicin, cyclophosphamide) and AC (doxorubicin and cyclophosphamide). The volume of patients receiving treatment has risen sharply over the last few years and many institutions have already moved away from the use of CMF for adjuvant therapy. The cost impact is therefore likely to be relatively limited.

The current cost of adjuvant therapy is estimated at just over £381,000 per annum for a Network with a population of 1.5 million. In the future it is anticipated that the proportion of patients receiving therapy will rise from 25% to 32%, accompanied by an increase in the proportion of patients receiving anthracycline-based therapy rather than CMF from 80% to 90%. The additional cost of therapy is estimated to be £109,000 per annum, an increase of 29%.

Extrapolating these results to England and Wales produces an estimate of current therapy costs of £13.2 million per annum. The additional cost of adjuvant chemotherapy is estimated to be around £3.8 million per annum, an increase of 29%.

The cost impact of switching between CMF and anthracycline-based regimens is expected to be relatively limited, given that much of this change appears to have already happened on a national basis. However an increase in the volume of patients receiving therapy may impact more dramatically on costs. In the high case scenario it is assumed that the proportion of patients receiving



chemotherapy in the future within each age group rises a further 10%, from 32% to 42%. The cost impact is estimated to be £9.1 million per annum, a rise of 69% over current levels.

## **Reduction in Long-term Follow-up**

The update states:

*“Routine long-term follow-up has not been shown to be effective and should cease. Networks should agree the period of time after which patients will be released from routine follow-up; this should not normally be more than three years except for women in clinical trials, for whom the trial protocol is likely to require long-term follow-up.”*

There are many thousands of asymptomatic women who have been treated for early breast cancer who are potentially eligible for long-term follow-up. An audit of UK follow-up practice in the early 1990's showed that only 15% of patients were discharged at five years, with this proportion rising to 43% at ten years. This situation does not appear to have changed dramatically. The impact of this policy for a particular institution will depend on their current follow-up policy, in terms of the duration and the frequency.

Frenchay Hospital in Bristol has recently adopted a policy of discharging patients from scheduled outpatient clinical review after five years, with two yearly mammography and open access. It is estimated that this policy will save 612 follow-up appointments, a cost saving of just under £50,000 per annum. This is equivalent to 204 new patient attendances. Based on these figures, and assuming that 15% of hospitals already operate a policy of five year follow-up, a similar policy adopted throughout England and Wales would save an estimated 54,500 follow-up appointments, a theoretical cost saving of £3.7 million per annum. A reduction in long-term follow-up allows more new outpatients to be seen within existing clinics, reducing pressure on waiting times targets for urgent (and non-urgent) referrals.

If this policy was to be extended to limit long-term follow-up to three years, the impact would be to further reduce the number of follow-up appointments. In a Cancer Centre treating 375 new patients per year, an additional 800 appointments would be saved, assuming that current policy is six monthly follow-up in year four and then annually in year five. This is equivalent to 275 new appointments and a potential financial saving of around £63,000 per annum. Extrapolation of this figure on a national basis would result in a reduction in the number of follow-up appointments of around 73,000 per annum. This amounts to a further cost-saving of £5.6 million per annum, assuming that all hospitals are starting from a position of five year follow-up.

These calculations do not take account of unscheduled open access appointments for those patients released from active follow-up. These will need to be monitored but are not expected to be large.

In reality the “savings” are unlikely to be realised. The saved clinic time is likely to be used in alternative ways, particularly for seeing new patients within existing clinics and reducing pressure on waiting times targets for urgent (and non-urgent) referrals.

## 1. Introduction

The School of Health and Related Research at the University of Sheffield (ScHARR) was commissioned to support the process of updating guidance on improving outcomes in breast cancer by analysing the potential cost implications of a small number of key issues raised by the guidance update. The 'Improving Outcomes' work is commissioned by the National Institute of Clinical Excellence.

The objective of this cost impact study is to address the cost consequences of the guidance update. Only the cost impact of changes in which the update is significantly different from the recommendations in the original guidance were considered.

There are only limited resources available for economic work in association with the updates, therefore a full cost impact study was not undertaken. A sub-group of the Editorial Board identified three issues where there was a significant new recommendation in the update. These issues were expected to impose the greatest financial consequences following implementation of the guidance. This exercise identified the cost implications of the guidance update for breast cancer for England and Wales in these three specific areas:

1. Use of bisphosphonates for treatment of bone metastases
2. Increased use of anthracycline-based regimens for adjuvant chemotherapy
3. Long-term follow-up of asymptomatic patients

The cost implications of the guidance outside these areas have not been considered.

The analysis does not aim to:

- assess the cost impact of all aspects of the updated guidance.
- give a definitive answer as to the cost implications of the update for specific Cancer Centres or Units but to produce an indication of the scale of costs involved.
- address in detail the training and workforce implications of the updated guidance.
- analyse the health outcome measures of meeting the recommendations.

## 2. Process and Methods

### 2.1 Literature and data searching

Literature searches were carried out on Medline in order to identify any existing costing exercises and audits of cancer activity. Members of the Editorial Board were contacted to identify any relevant material.

Very little costing data was found in the literature for the UK. There are some American studies of costs, but treatment patterns and cost structures are considerably different in the USA than from in the UK and therefore little weight has been attached to them.

## **2.2 Discussions with clinicians and other key professionals**

Advice from clinicians on the Editorial Board was sought to ensure that appropriate assumptions were made in the modelling of future activity, to identify data sources and to assist in the interpretation of data. A number of other clinicians were contacted to assist in the cost analysis, where appropriate.

## **2.3 Cost analysis and modeling**

For each of the key issues an estimate of the national cost consequences has been made. The approach adopted for each issue is detailed in the relevant section.

# **3. Cost Impact Analysis**

## **3.1 Use of bisphosphonates for treatment of bone metastases**

The guidance update states that:

*“The symptoms of bone metastases may respond to systemic interventions particularly hormone therapy and treatment with bisphosphonates” and “they should be given for as long as skeletal disease remains an important clinical problem.”*

### **3.1.1 Introduction**

Bone metastases associated with breast cancer disease result in considerable morbidity including bone pain, pathological fractures, spinal cord compression, hypercalcemia and reduced quality of life.

In the UK about 9,000 women with breast cancer develop bone metastases each year.<sup>1</sup>

The median survival for women from the first detection of metastatic disease is approximately 18-24 months.<sup>2</sup>

Both intravenous pamidronate and oral clodronate have been shown to be effective in reducing bony complications in patients with metastatic breast cancer. The evidence relating to the benefits of oral clodronate is less extensive than that for intravenous pamidronate. There is no evidence to suggest that bisphosphonates improve survival.

The optimum duration of therapy is as yet unclear. Average treatment duration is currently around six months.<sup>3</sup> Current treatment duration is however often too short for patients to obtain full benefit (R Coleman, personal communication). The recent BASO guidelines suggest that “where possible treatment with bisphosphonates should be continued indefinitely”.<sup>1</sup>

Bisphosphonates appear to be well tolerated. With oral preparations gastrointestinal intolerance is the most common reason for non-compliance, but placebo controlled trials found no difference between active therapy and placebo.

### 3.1.2 Resource implications

The impact of the guidance is likely to fall in two areas:

- a potential increase in the volume of patients receiving bisphosphonate therapy, given that not all patients who could benefit from these drugs are currently prescribed them.
- a potential increase in the duration of therapy.

The BASO guidelines suggest that treatment should be continued indefinitely.<sup>1</sup> Therefore the increase in the volume of patients receiving bisphosphonates may well be accompanied by an increase in duration of therapy.

### 3.1.3 Review of evidence on cost-effectiveness

No UK cost utility studies looking at the use of bisphosphonates in breast cancer patients with metastatic bone disease have been identified.

Dranitsaris *et al* reported a cost utility analysis performed from a Canadian health care system perspective to estimate the incremental cost effectiveness of pamidronate in patients with advanced breast cancer.<sup>4</sup> Total hospital resource consumption was collected for 25 patients who were bisphosphonates naïve and had developed skeletal related complications. A decision analytic model was used to compare total costs in the pamidronate patients compared to patients in a no treatment alternative. The analysis showed that pamidronate had a high drug acquisition cost but provided patients with a substantial quality adjusted survival benefit at a reasonable cost to the Canadian Health care.

Hillner *et al* in a post hoc economic assessment of the two manufacturer-sponsored multinational trials showed that the costs of pamidronate were projected to greatly exceed the cost savings associated with preventing skeletal related events.<sup>2</sup> Using assigned utility values that reflect overall quality of life the projected costs per added QALY with pamidronate were higher than those of the most commonly accepted medical interventions. However care must be taken when interpreting cost data from the USA health care setting. In particular the cost of treatment with pamidronate in this study is considerably higher than the cost in the UK.

Hillner *et al* suggest that more research is needed to improve the estimates of the direct and indirect cost consequences of bony complications of breast cancer.<sup>2</sup>

### 3.1.4 Estimation of the cost impact

#### Cost of pamidronate

Pamidronate is given as a monthly 90 minute infusion. The drug cost is approximately £185 per infusion (Pharmacy, Weston Park Hospital, Sheffield, personal communication). This cost is based on BNF prices and includes VAT. It should be noted that prescriptions that are dispensed from community pharmacies are VAT exempt. In addition individual institutions may receive a discount on BNF prices. These discounts are agreed locally and are often short term and have not been taken into account.

The administration of pamidronate requires a day case visit once every 4 weeks. The cost of a day case visit is assumed to be £125 (Pharmacy, Weston Park Hospital, Sheffield, personal communication). Therefore the cost of a day-case visit for each infusion is assumed to result in a cost per infusion of £310.

However this is likely to be an overestimate of administration costs given that pamidronate may be given with chemotherapy which requires a day case attendance, say for six months of a patients treatment. In addition these patients would be attending for an outpatient visit every two to three months for follow-up which will be incorporated into the day-case visit. For patients receiving chemotherapy the administration cost is assumed to be zero in the first six months. For treatment durations above six months it is assumed that the average monthly administration cost is £97 per infusion for month seven onwards. This cost takes into account the cost saving from an avoided outpatient visit once every three months. For those patients not receiving chemotherapy the administration cost is assumed to average £97 per infusion every month. Assuming that 50% of patients receive chemotherapy the average administration cost is £48 for six months treatment and £81 for 18 months treatment.

The cost of pamidronate is therefore assumed to be £233 per infusion, assuming six months treatment and £266 per infusion, assuming 18 months treatment.

#### Cost of clodronate

Clodronate is an orally administered drug. The cost of clodronate is approximately £210 per month. The cost of clodronate includes VAT although it should be noted that prescriptions that are dispensed from community pharmacies are VAT exempt. In addition individual institutions may receive a discount on BNF prices. These discounts are agreed locally and are often short term and have not been taken into account.

Clodronate is generally not approved for GP prescription, therefore patients have to attend monthly for an outpatient visit and prescription. It is assumed patients would normally attend an outpatient appointment once per quarter and therefore patients on clodronate receive two additional outpatient appointments per quarter. The cost of an outpatient appointment is assumed to be £85 (Weston Park Hospital, Sheffield, personal communication). The average monthly administration cost is therefore assumed to be £57.

The cost per month of oral clodronate is estimated to be £267.

## Cost impact for a typical Network

The results are presented for a typical Cancer Network with a population of 1.5 million.

About 9,000 women with breast cancer develop bone metastases each year in the UK. Therefore approximately 230 patients are likely to present with bone metastases per annum, based on a population of 1.5 million.

Targetting of treatment to sub-groups who might benefit is recommended by the BASO guidelines.<sup>1</sup> Guidelines already exist for prioritisation of long-term bisphosphonate treatment. For example local guidelines developed at the Yorkshire Cancer Research Campaign (YCRC) prioritise patients as high, moderate or low, based on a number of factors, including disease extent, bone morbidity and ECOG status. High priority patients account for approximately two-thirds of this group (R Coleman, personal communication).

It is estimated that 50% of these high priority patients are currently receiving bisphosphonates (R Coleman, personal communication). This is supported by an audit of bisphosphonate usage undertaken by Novartis which suggested that around 60% of eligible patients did not receive treatment in 2000.<sup>3</sup> This implies that around 76 breast cancer patients with bone metastases are likely to receive bisphosphonate therapy in a typical network.

It is assumed that 75% of prescriptions are for pamidronate. The average treatment duration is around six months.<sup>3</sup>

Based on a cost per infusion for pamidronate of £233 and the cost per month for clodronate of £267, the average cost per patient assuming a six month treatment duration is £1,450. The current cost of treatment for a typical Cancer Network is estimated to be approximately £110,200 per annum.

A central scenario has been defined, assuming that 100% of high priority patients receive bisphosphonates and the average treatment duration is 15 months. The cost of treatment is estimated to rise by £340,000 an increase of just over 300%.

### Sensitivity analysis

Key parameters were tested using sensitivity analysis to determine the extent to which variations in these parameters influenced the results (Table A.1).

Sensitivities 1 and 2 demonstrate the impact of changing the proportion of high priority patients treated whilst the duration of treatment remains at current levels. Sensitivities 3 to 5 demonstrate the impact of changing the duration of treatment whilst the proportion of high priority patients treated remains at current levels.

Sensitivity 6 assumes that 100% of high priority patients receive bisphosphonates with an average treatment duration of 18 months. This figure is likely to be an upper ceiling based on leading clinical opinion of best practice.

Sensitivity 7 demonstrates the impact of varying the proportion of patients prescribed pamidronate and clodronate.

**Table A.1 Sensitivity analysis for the use of bisphosphonates**

	<b>% of high priority patients treated</b>	<b>Duration of treatment (months)</b>	<b>% of patients receiving pamidronate</b>	<b>Cost (£1000s)</b>	<b>Cost Impact (£000s)</b>	<b>% change in cost</b>
Current	50	6	75	110		
Basecase	100	15	75	601	490	445
Sen 1	75	6	75	165	55	50
Sen 2	100	6	75	220	110	100
Sen 3	50	12	75	237	127	115
Sen 4	50	15	75	300	190	173
Sen 5	50	18	75	364	254	230
Sen 6	100	18	75	727	617	560
Sen 7	75	15	25	606	495	449

The sensitivity analysis demonstrates that the duration of treatment is likely to have the greatest impact on future treatment costs. Combining this with an increase in the volume of patients results in a further increase in predicted future costs.

### Cost impact for England and Wales

Extrapolating these estimates to England and Wales, based on a population of 52.7 million, the current cost of treatment is estimated at approximately £3.9 million.

The central scenario assumes that 75% of high priority patients receive bisphosphonates and the average treatment duration is 15 months. The future cost of treatment is therefore estimated to rise by £17.2 million, an increase of 445%.

By assuming that 100% of high priority patients receive bisphosphonates and the average treatment duration is 18 months the cost of treatment is estimated to rise to approximately £25.6 million, an increase of £21.7 million (560%). This represents an upper ceiling.

### Potential cost savings

Treatment costs will in part be offset by reduced incidence of fractures, radiotherapy for bone pain, surgery to bone, and treatment of hypercalcaemia. Several placebo controlled randomised studies in women with skeletal metastases and breast cancer have shown significant reductions (25 to 50%) in skeletal morbidity (pathological fractures, bone pain requiring skeletal radiotherapy and hypercalcemia).

The Cancer Care Ontario Practice Guidelines on the use of bisphosphonates in patients with bone metastases from breast cancer presented a meta analysis which showed that once bone metastases were present, the use of oral clodronate or intravenous pamidronate can reduce skeletal events and pain when used concomitantly with first-line chemotherapy or hormones.<sup>5</sup> The overall risk ratios were 0.72 (95% confidence interval 0.60 to 0.87, p=0.0006) for

fractures and 0.61 (95% confidence interval 0.51 to 0.73,  $p < 0.00001$ ) for radiotherapy, demonstrating a significant effect in favour of treatment with bisphosphonates.

Cook and Major have recently proposed the use of a general random-effects model to accommodate variation in complication rates between different patients.<sup>6</sup> On this basis the rate of skeletal complications is estimated to fall by 32% with pamidronate compared with placebo, among patients with comparable survival times. They have suggested that the use of the “events-per-person-years” methodology applied in earlier studies, which assumes that all patients within each arm of the study experience skeletal complications at the same rate, is inappropriate given the high variability of the rate of occurrence of bone complications between patients.

The estimation of the benefits is complex and open to uncertainty. However it is clear that the cost savings will not be trivial. The number of total skeletal-related events was 630 for 195 patients in the placebo arm of Aredia Breast Cancer Protocol 18 (patients receiving concomitant chemotherapy) and 627 for 190 patients in the placebo arm of Aredia Breast Cancer Protocol 19 (patients receiving concomitant hormonal therapy). The cost of treating adverse events is high. Bruce *et al* reported the cost of treating vertebral fractures at £2,126, the cost of treating arm, leg and rib fractures as £4,762, £7,451 and £388 respectively and the cost of treating severe hypercalcaemia as £1,730.<sup>7</sup> More research is needed to derive estimates of the direct and indirect cost consequences of bony complications in breast cancer.

### Other issues

A new intravenous bisphosphonate, zolidronate, is expected to receive its licence in the UK later in 2002. However the cost of the drug is similar to pamidronate and therefore this will not impact significantly on these calculations.

## 3.2 Use of anthracycline-based regimens for adjuvant chemotherapy

The guidance update recommends that:

*“Women at intermediate or high risk of recurrence, who have not had neo-adjuvant chemotherapy, should normally be offered four to eight cycles of multiple-agent chemotherapy which includes anthracyclines.”*

### 3.2.1 Introduction

Adjuvant chemotherapy for the treatment of early breast cancer produces a highly significant reduction in recurrence and morbidity in women under 70 years of age.

The benefits of polychemotherapy are age-related.<sup>8</sup> The Early Breast Cancer Trialists' Collaborative Group overview concluded that polychemotherapy produces a 35% reduction in the risk of recurrence in women under 50 years old and a 20% reduction in women aged 50 to 69. There is little data concerning the potential benefits of adjuvant chemotherapy in women over 70.



Compared with CMF, anthracycline-containing regimens have been shown to reduce recurrence by 12% ( $p=0.006$ ) and increased 5-year absolute survival rates from 69% to 72% ( $p=0.02$ ).<sup>8</sup>

In recent years there has been a move towards anthracycline-based therapy, but the results of a survey of UK oncology centres showed that CMF was still used in many centres in 1999.<sup>9</sup>

Classical CMF, the schedule published by Bonnadonna *et al*, uses 14 days of oral cyclophosphamide, with intravenous methotrexate and fluorouracil administered on days one and eight of a 28 day cycle.<sup>10</sup> However the survey of UK oncology centres identified 36 different CMF schedules in use.<sup>9</sup> Some Centres, particularly in Scotland, have moved towards a three weekly intravenous CMF regimen. Patients do not need to attend the hospital as frequently but the dose intensity of the treatment is reduced and there is indirect evidence that “lower” dose three weekly schedules produce inferior outcomes compared to conventional CMF regimens.<sup>11</sup>

Anthracycline-based regimens are increasingly being used for adjuvant therapy in the UK. Common regimens include FEC (fluorouracil, epirubicin, cyclophosphamide) and AC (doxorubicin and cyclophosphamide).

### 3.2.2 Resource implications

The impact of the guidance is likely to fall in two areas:

- a potential increase in the volume of patients offered polychemotherapy in primary therapy.
- a potential rise in the proportion of these patients receiving anthracycline-based regimens rather than CMF.

However the additional costs of adjuvant treatments for primary breast cancer may be balanced by a reduction in treatment costs for recurrence and for advanced disease.

### 3.2.3 Review of evidence on costs and cost-effectiveness

No UK cost or cost utility studies looking at the use of adjuvant chemotherapy in patients with early breast cancer have been identified.

### 3.2.4 Cost impact analysis

#### Volume of patients receiving adjuvant chemotherapy

The proportion of patients with stage I and stage II breast cancer receiving chemotherapy in Northern and Yorkshire in 1999 was as follows (personal communication, NYCRIS):

Under 50 years:	59%
Aged 50-69:	27%
Aged 70+:	2%

It is assumed that this reflects current practice on a national basis.

#### Regimens used

A number of clinicians and pharmacists were contacted to discuss the regimens currently offered to patients in their institution. Based on these discussions it appears that many institutions have already moved away from the use of CMF for adjuvant therapy. A significant proportion of these institutions now offer only anthracycline-based therapy to the majority of their patients. In these institutions CMF is reserved for a small proportion of more fragile patients with co-morbidities.

The most common anthracycline-based regimens are AC (four cycles) and FEC (six or eight cycles). Some institutions use only one anthracycline-based regimen for all patients, others use different regimens for different patients.

#### Costs

##### *CMF (cyclophosphamide, methotrexate and 5-fluorouracil)*

The classical CMF schedule has been costed. Drug costs were made available by (Jon Karnon, personal communication) and the cost of administration is based on a day case cost of £123.37 (Weston Park Hospital, Sheffield, personal communication).

Schedule: Cyclophosphamide 100mg/m<sup>2</sup> days 1-14, Methotrexate 40mg/m<sup>2</sup> days one and eight iv, 5-Fluorouracil 600mg/m<sup>2</sup> days one and eight iv four week cycle for six courses.

##### *Anthracycline-based Regimens*

Two commonly used anthracycline-based schedules have been costed, based on cost data supplied by Weston Park Hospital Pharmacy.

- 1) FEC (fluorouracil, epirubicin, cyclophosphamide)  
Schedule: fluorouracil 600mg/m<sup>2</sup>, epirubicin 60mg/m<sup>2</sup>, cyclophosphamide 600mg/m<sup>2</sup> given every 21 days for 6-8 cycles.
- 2) AC (doxorubicin-cyclophosphamide)

Schedule: Doxorubicin 60mg/m<sup>2</sup> iv and cyclophosphamide, 600mg/m<sup>2</sup> iv given on day 1 of 3 week cycle for 4 cycles (or 6 cycles).

The costs are shown in Table A.2

**Table A.2 Cost of adjuvant chemotherapy regimens**

	CMF	Anthracycline-based	
		FEC	AC
Drugs	£ 34.61	£ 250.00	£ 270.00
Assumed discount	30%	30%	30%
Discounted drug costs	£ 24.23	£ 175.00	£ 189.00
Anti-emetics	£ 52.67	£ 43.00	£ 43.00
Administration	£246.74	£123.37	£123.37
<b>Total cost per cycle</b>	£ 323.64	£ 341.37	£ 355.37
No. of cycles	6	6	4
Cost per Patient	£1,941.82	£2,048.22	£1,421.48

Note 1: The costs of disposables and tests have been excluded.

Note 2: The drug cost of AC and FEC are based on discounted BNF prices (with VAT added) assuming a 30% discount. Discounts are likely to vary between institutions.

The relatively low drug cost for CMF is offset by higher administration costs. Classical CMF requires two visits to clinic during the four week cycle, whilst the anthracycline-based regimens only require one visit per three week cycle.

### Cost impact for a typical Cancer Network

The incidence of breast cancer in England and Wales in 1997 was 33,100, Approximately 87% of patients present with early stage cancer (stage I or stage II).<sup>12</sup> A typical cancer network with a population of 1.5 million would therefore expect approximately 830 new patients to present with stage I or stage II breast cancer per annum.

In 1998 20.5% of all women presenting with breast cancer in England were aged under 50, 44.5% were aged between 50-69 and 35% were aged 70 plus.<sup>15</sup> It is assumed that the proportion of women presenting with early breast cancer is the same as the proportions for all women with breast cancer.

Based on 1999 data from the Northern and Yorkshire Cancer Registry it is assumed that 59% of women aged under 50, 27% of women aged 50 to 69 years and 2% of women aged 70 and over receive adjuvant therapy (personal communication, NYCRIS).

In the base case scenario it is assumed that 20% of patients receiving adjuvant chemotherapy currently receive a CMF regimen. The remaining patients are assumed to receive either FEC (two-thirds of remaining patients) or AC (one third of remaining patients).

The current cost of adjuvant therapy is estimated at approximately £381,000 for a Network with a population of 1.5 million. If only drug costs are considered (including anti-emetics) the current cost is approximately £219,000.

Over the last few years there has been a significant rise in the proportion of women receiving adjuvant chemotherapy. Recent data from NYCRIS suggests that approximately 25% of patients receive adjuvant chemotherapy (personal communication, NYCRIS). This sharp rise is not expected to continue. The proportion of women receiving adjuvant therapy in three to four years time is assumed to rise moderately to 32% (66.6%, 33.3% and 10% for women aged under 50 years, aged between 50 and 69 years, and aged 70 years and over respectively). This results in an additional 60 patients receiving therapy.

In addition a greater proportion of therapy, 90%, is assumed to be anthracycline-based.

The potential impact on adjuvant chemotherapy costs are shown in Table A.3.

**Table A.3 Cost impact of anthracycline-based therapy for a typical Cancer Network**

Chemo Regimen	% of patients-current	% of patients-future	Change in volume	Cost per patient (£)	Total cost impact (£)	% change in cost
CMF	20	10	- 14	1,942	- 28,151	
AC	27	30	25	1,421	35,349	
FEC	53	60	50	2,048	101,870	
Overall	100	100			109,069	29%

The additional cost of chemotherapy is estimated to be £109,000 an increase of 29%, based on an increase in the proportion of patients receiving anthracycline-based therapy from 80% to 90%, and an additional 60 patients receiving treatment.

Based on drug costs alone the current cost of adjuvant therapy is estimated at approximately £213,000 for a Network with a population of 1.5 million and the cost impact is estimated to be £81,000, a rise of 38%.

### Sensitivity analysis

Key parameters were tested using sensitivity analysis to determine the extent to which variations in these parameters influenced the results (Table A.4).

Sensitivities 1 and 2 demonstrate the impact of changing the proportion of patients receiving treatment with adjuvant chemotherapy, whilst other parameters remain the same. Sensitivities 3 and 4 demonstrate the impact of changing the proportion of patients receiving CMF in the future whilst other parameters remain at current levels. Sensitivity 5 and 6 demonstrate the impact of assumptions regarding the type of anthracycline-based therapy used in the future.

Sensitivity 7 combines the impact of increasing the proportion of patients receiving treatment with adjuvant chemotherapy from the basecase of 32% to 42%, and all patients in the future receiving the more expensive anthracycline-based regimen, FEC.

**Table A.4 Sensitivity analysis for the use of anthracycline-based therapy for a typical Cancer Network**

	% of patients receiving adjuvant chemotherapy	% of patients receiving CMF	% of patients receiving FEC	Cost (£1000s)	Cost Impact (£000s)	% change in cost
Current	25	80	66.7	381		
Basecase	32	90	66.7	490	109	29
Sen 1	25	90	66.7	379	-2	-1
Sen 2	42	90	66.7	644	262	69
Sen 3	32	80	66.7	493	112	29
Sen 4	32	100	66.7	488	106	28
Sen 5	32	90	100.0	540	159	42
Sen 6	32	90	0.0	391	9	2
Sen 7	42	90	100.0	709	328	86

### Cost impact for England and Wales

Extrapolating these results to England and Wales produces an estimate of current therapy costs of £13.3 million (£7.6 million for drug costs alone). The additional cost of chemotherapy is estimated to be around £3.8 million per annum, an increase of 29%, based on an increase in the proportion of patients receiving anthracycline-based therapy from 80% to 90%, and an additional 2,092 patients receiving therapy.

**Table A.5 Cost impact of anthracycline-based therapy for England and Wales**

Chemo Regimen	% of patients-current	% of patients-future	Change in volume	Cost per patient (£)	Total cost impact (£000s)	% change in cost
CMF	20	10	- 505	1,942	- 980	
AC	27	30	865	1,421	1,230	
FEC	53	60	1,731	2,048	3,545	
Overall	100	100			3,796	29

Based on drug costs alone the current cost of adjuvant therapy is estimated at approximately £7.4 million for a Network with a population of 1.5 million and the cost impact is estimated to be £2.9 million, a rise of 38%.

### Sensitivity analysis

Sensitivities 1 and 2 demonstrate the impact of changing the proportion of patients receiving treatment with adjuvant chemotherapy, whilst other parameters remain the same. Sensitivities 3 and 4 demonstrate the impact of changing the proportion of patients receiving CMF in the future whilst other parameters remain at current levels. Sensitivity 5 and 6 demonstrate the impact of assumptions regarding the type of anthracycline-based therapy used in the future.

Sensitivity 7 combines the impact of the increasing the proportion of patients receiving treatment with adjuvant chemotherapy from the basecase of 32% to 42%, and all patients receiving in the future receiving the more expensive anthracycline-based regimen, FEC.

Results are given in table A.6.

**Table A.6 Sensitivity analysis for the use of anthracycline-based therapy in England and Wales**

	% of patients receiving adjuvant chemotherapy	% of patients receiving CMF	% of patients receiving FEC	Cost (£ m)	Cost Impact (£ m)	% change in cost
Current	25	80	66.7	13.3		
Basecase	32	90	66.7	17.1	3.8	29
Sen 1	25	90	66.7	13.2	-0.1	-1
Sen 2	42	90	66.7	22.4	9.1	69
Sen 3	32	80	66.7	17.2	3.9	29
Sen 4	32	100	66.7	17.0	3.7	28
Sen 5	32	90	100.0	18.8	5.5	42
Sen 6	32	90	0.0	13.6	0.3	2
Sen 7	42	90	100.0	24.7	11.4	86

The sensitivity analysis shows that the proportion of patients receiving chemotherapy is likely to have the largest impact on future costs. Over the last few years there has been a significant rise in the proportion of women receiving adjuvant chemotherapy. Recent data from NYCRIS suggests that approximately 25% of patients receive adjuvant chemotherapy. This sharp rise is not expected to continue. Therefore 42% is considered to be an upper ceiling.

## Discussion

The drug costs used are based on discounted BNF prices. The discount is assumed to be 30% across all regimens. Individual institutions may receive different levels of discount on BNF prices. The costs include VAT, although it should be noted that prescriptions that are dispensed from community pharmacies are VAT exempt.

It should be noted that for institutions currently using a three weekly CMF regimen baseline treatment costs will be lower price and therefore the move to anthracycline-based therapy will have a greater cost impact.

## Reduction in recurrences and progression to advanced disease

The additional costs of adjuvant treatments for primary breast cancer may be balanced by a reduction in treatment costs for recurrence and for advanced disease.

Local recurrence rates up to 25% have been reported after 25 years of follow-up following breast conserving treatment. In approximately 15% of cases the local recurrence is irresectable and the patient will eventually die from the disease. The other patients can be treated by salvage mastectomy.<sup>14</sup>

The mean cost of hospital care for patients with advanced breast cancer was calculated to be £7,620 (range: £317 - £27,860) by Richards *et al* in 1993.<sup>15</sup> In 1998 Wolstenholme *et al* estimated a mean total four year cost of £4,646 (SD 3,820) for diagnosis and treatment of patients with advanced breast cancer.<sup>16</sup>

These cost savings are not taken into account.

### 3.3 Long-term follow-up

The guidance update states:

*“Routine long-term follow-up has not been shown to be effective and should cease. Networks should agree the period of time after which patients will be released from routine follow-up; this should not normally be more than three years except for women in clinical trials, for whom the trial protocol is likely to require long-term follow-up.”*

#### 3.3.1 Introduction

In 1997 the annual incidence of breast cancer in England and Wales was 33,100.<sup>17</sup> Five year survival for stages I and II is approximately 80%.<sup>18</sup> Therefore there are many thousands of women who are potentially eligible for long-term follow-up and accommodating this need is a significant resource issue for the NHS.

In the UK most follow-up visits will include history, physical examination and mammography on the contralateral breast and/or the reconstructed breast. Other procedures are not generally carried out.<sup>19</sup>

An audit of UK follow up practice in 1995, showed that standard practice was for follow-up to occur within an oncology clinic, three to four monthly for the first two years, then six monthly for years three and four and then annually. Only 15% of patients were discharged at five years, with this proportion rising to 43% at ten years.<sup>19</sup> After the tenth year a proportion will continue annually. The audit also showed that GP follow-up accounted for less than 3% of all follow-up.

Following discussion with a number of clinicians throughout the country it appears that there has been little change in follow-up policy, following publication of the original guidance. There is however some variation in practice. A number of examples of changes in follow-up practice, in terms of reduction in the duration of long-term follow-up and a move towards nurse-led clinics have been highlighted by the Cancer Services Collaborative. However these are considered to be the exception rather than the rule.

The guidance update is, however, more prescriptive, in particular providing a specific recommendation for the duration of long-term follow-up.

### 3.3.2 Resource implications

#### Reduction in the duration of long-term follow-up

The recommendation that long-term follow-up is restricted to two to three years may have a major impact on the number of follow-up appointments for breast cancer patients, assuming that the guidance is fully implemented. The impact of this policy will depend on the current follow-up policy, in terms of the duration and the frequency.

In many hospitals long-term follow-up still continues beyond five years and there is the potential to drastically reduce the number of follow-up appointments. Even in those hospitals where long-term follow-up has been restricted to five years there is the potential for further cost savings. A reduction in long-term follow-up allows more new outpatients to be seen within existing clinics, reducing pressure on waiting times targets for urgent referrals.

#### Nurse-led clinics

In recent years there has been some move towards nurse-led follow-up clinics. Early indications are that these increase throughput, allowing more follow-up appointments to be seen per week.

#### GP Follow-up

A further step would be to move the location of follow-up away from hospital-based clinics towards the GP setting. This has the advantage of freeing up hospital clinics to allow more new patients to be seen. It may also have an economic benefit in terms of providing a cheaper alternative to consultant-led follow-up. However the capacity of GPs to take on this further workload is uncertain.

### 3.3.3 Review of evidence on costs and cost-effectiveness

#### Duration of long-term follow-up

No randomised controlled trial evidence on the costs or cost effectiveness of reducing long-term follow-up has been identified.

A case study from Frenchay Hospital in Bristol has been publicised by the Cancer Services Collaborative. Prior to the introduction of the new policy, recurrence-free patients more than five years from diagnosis and treatment occupied 612 (11.8%) of outpatient appointments. The hospital adopted a policy of discharging patients from scheduled outpatient clinical review after five years, with two-yearly mammography and open access. It is estimated that this policy will save 612 follow-up appointments, a cost saving of £48,960 per annum (S Cawthorn, personal communication).

#### Nurse-led clinics

No randomised controlled trial evidence on the costs or cost effectiveness of nurse-led clinics has been identified.



Earnshaw and Stephenson provided a description of a nurse-led clinic at Gloucestershire Royal Hospital.<sup>20</sup> After special training a nurse practitioner ran an independent clinic for follow-up of patients with breast disease. In the first two years of the service 382 clinic visits were recorded. Follow-up after cancer was standard: three-monthly for two years then six-monthly until five years. The nurse practitioner reviewed 62% of patients alone but involved the consultant surgeon in the remainder. No significant lesion was missed in these patients. The nurse led breast follow-up clinic was originally designed to increase the throughput of patients but proved to have many other advantages such as allowing longer appointments than those in the general clinic. No data on efficiency gains were provided.

At Frenchay Hospital in Bristol the introduction of a nurse-led clinic has freed up consultant time and allowed the percentage of patients to be seen within the national two-week wait target to be increased. An extra five patients per clinic have been seen, an increase of 20% (S Cawthorn, personal communication).

### GP follow-up

Grunfeld *et al* undertook a randomised controlled trial (RCT) comparing primary care centred follow-up of breast cancer patients with the current standard practice of specialist centred follow-up in the UK.<sup>21</sup> This study showed no increase in delays in diagnosing recurrence and no increase in anxiety or deterioration in health-related quality of life. An economic evaluation of the two schemes of follow-up was conducted concurrent with the RCT.<sup>22</sup> Process measures of the quality of care such as frequency and length of visits were superior in primary care. Costs to patients and to the health service were lower in primary care. The average cost per patient in the GP group and hospital group were £64.70 (SD £42.8) and £195.10 (SD £107.40).

A Canadian five year study of similar design is currently in progress and will report in around two year's time (E Grunfeld, personal communication). If the results of this study support the UK study there will certainly be an economic case for GP follow-up. However there would also need to be a GP willingness and capacity to take on this extra workload. This is currently unknown.

### 3.3.4 Cost impact analysis

There are two key issues relating to the future role of hospital follow-up. Firstly questions relating to the most appropriate location and form of follow-up (i.e. primary care led follow-up versus consultant-led follow-up in a hospital clinic) and secondly questions concerning the value of any form of routine long-term follow-up.

The guidance update provides a specific recommendation that the duration of follow-up “*should not normally be longer than three years*”. However no specific recommendations about the role of nurse-led follow-up or GP follow-up are made in the update. Following discussion with a number of clinicians it was clear that there is no clarity about what model(s) might replace the existing consultant-led follow-up and how quickly these models may evolve. This area is likely to evolve within the various Networks in a somewhat pragmatic and variable fashion. The issue is likely to be considered by individual Cancer Networks. A costing exercise is neither feasible nor necessary. The cost impact

study therefore considers only the larger issue of the reduction in the duration of long-term follow-up.

### Reduction in the duration of long-term follow-up

At Frenchay Hospital in Bristol the introduction of a policy of discharging patients from scheduled outpatient clinical review after five years, with two yearly mammography and open access, has resulted in more patients being seen. The increase in appointments is estimated to be approximately 20% (S Cawthorn, personal communication). Based on an outpatient appointment cost of £80, it has been estimated that this policy resulted in a cost saving of just under £50,000 per annum (S Cawthorn, personal communication). Extrapolation of this figure on a national basis would result in a cost-saving of £4.4 million, assuming that all hospitals are in a similar starting position to Frenchay Hospital. However this may over-estimate the potential savings as some hospitals have already moved to five year follow-up and have already achieved these savings.

The central scenario, which takes a more conservative view, assumes that 15% of hospitals already operate a policy of five year follow-up<sup>19</sup> and that the potential cost saving is therefore reduced to £3.7 million.

If this policy were to be extended to restrict long-term follow-up to three years, the impact would be to reduce the number of follow-up appointments by an additional 818. This figure is based on a Breast Care Unit treating 375 new patients per year and assuming that current policy is six monthly follow-up in year four and then annually in year five. This is equivalent to 275 new appointments. Assuming a cost per follow-up appointment of £80 this results in a potential financial saving of £63,000.

Extrapolation of this figure on a national basis would result in a reduction in the number of follow-up appointments of around 73,000. This amounts to a further cost-saving of £5.6 million, assuming that all hospitals are starting from a position of five year follow-up. This results in a total cost saving of £9.3 million.

In hospitals where the current follow-up policy is to follow up patients annually in year four and year five, the potential reduction in the number of follow-up appointments is 544. This is equivalent to approximately 180 new appointments at a cost saving of £42,000.

These calculations do not take account of unscheduled open access appointments for those patients released from active follow-up. These will need to be monitored but are not expected to be large.

### Discussion

Although a financial value had been placed on the reduction of follow-up appointments, the savings are not expected to be realised. The saved clinic time is likely to be used in alternative ways, particularly for seeing new patients within existing clinics, reducing pressure on waiting times targets for urgent (and non-urgent) referrals.

Reluctance to move away from long-term follow-up has been demonstrated since the mid-90s and therefore a rapid change in practice may not be achieved. Indeed there are strong opponents to reducing long-term follow-up.<sup>23</sup>

There have, however, been recent attempts to stimulate changes in follow-up policy through the Cancer Services Collaboratives. A recent initiative to roll out the five year follow-up policy successfully implemented by Frenchay Hospital is currently in progress in the South and West region and is being extended to a national basis.<sup>24</sup> This may well increase the momentum for change.

Nurse-led follow-up may also offer an opportunity to free up consultant time to see new patients. However in many organisations it is likely to require investment in a nurse practitioner and/or training of an existing nursing sister to allow this to happen. The nurse-led clinic at Gloucestershire Royal Hospital proved to have many advantages. It proved popular with patients who see the same person on each clinic visit, allowing them to build up long-term relationships. Appointments were longer than those in the general clinic and therefore patients could raise other issues such as lymphoedema. Subject to careful supervision it may offer an attractive option for follow-up.

## 4. Conclusion

This cost impact study addressed the cost consequences of the guidance in three specific areas:

1. Use of bisphosphonates for treatment of bone metastases
2. Increased use of anthracycline-based regimens for adjuvant chemotherapy
3. Long-term follow-up of asymptomatic patients

It is estimated that the additional cost for caring for patients with breast cancer in these areas will be around £21.0 million per annum. Most of this additional cost will arise from a projected increase in the use of bisphosphonates as a result of more patients receiving treatment and an increase in the duration of treatment. This rise may, in part, be offset by reductions in skeletal-related events (for instance, reduction in the number of fractures and a reduction in the need for radiation for bone pain) resulting from the use of bisphosphonates. The cost savings, although not known with certainty, are not likely to be trivial. Further research is needed to estimate these cost savings.

There is also the potential to “save” an estimated £8.7 million per annum from reduced long-term follow-up appointments. Although a financial value has been placed on this figure, the savings are not expected to be realised. The “saved” clinic time is likely to be used in alternative ways, particularly for seeing new patients within existing clinics, reducing pressure on waiting times targets for urgent (and non-urgent) referrals.

## References for Appendix 1

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## Appendix 2

# Composition of Research Review and Critical Appraisal Teams

Heather McIntosh and Kate Misso undertook the review work and literature searches with support from staff at the NHS Centre for Reviews and Dissemination, University of York. The project was co-ordinated by Alison Eastwood and Jos Kleijnen.

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Chrissie Lane	Clinical Services Manager Oncology, Cookridge Hospital, Leeds.
Dr Geoffrey Parkin	Consultant Radiologist, Chapel Allerton Hospital, Leeds.
Jacqui Todd	Clinical Lymphoedema Specialist, Cookridge Hospital, Leeds.
Prof Lindsay Turnbull	Scientific Director, Centre for MR Investigations, Hull Royal Infirmary, Hull.
Dr Ruth Warren	Department of Radiology, School of Clinical Medicine, University of Cambridge.
Dr Robin Wilson	Clinical Director, Breast Directorate, Nottingham International Breast Education Centre, Nottingham.