Early breast cancer

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Adoption of urbanised lifestyles together with changes in reproductive behaviour might partly underlie the continued rise in worldwide incidence of breast cancer. Widespread mammographic screening and effective systemic therapies have led to a stage shift at presentation and mortality reductions in the past two decades. Loco-regional control of the disease seems to affect long-term survival, and attention to surgical margins together with improved radiotherapy techniques could further contribute to mortality gains. Developments in oncoplastic surgery and partial-breast reconstruction have improved cosmetic outcomes after breast-conservation surgery. Optimum approaches for delivering chest-wall radiotherapy in the context of immediate breast reconstruction present special challenges. Accurate methods for intraoperative assessment of sentinel lymph nodes remain a clinical priority. Clinical trials are investigating combinatorial therapies that use novel agents targeting growth factor receptors, signal transduction pathways, and tumour angiogenesis. Gene-expression profiling offers the potential to provide accurate prognostic and predictive information, with selection of best possible therapy for individuals and avoidance of overtreatment and undertreatment of patients with conventional chemotherapy. Short-term presurgical studies in the neoadjuvant setting allow monitoring of proliferative indices, and changes in gene-expression patterns can be predictive of response to therapies and long-term outcome.

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Introduction

Breast cancer remains the most common malignancy in women worldwide and is the leading cause of cancer-related mortality.[1] More than 1·2 million cases are diagnosed every year, affecting 10–12% of the female population and accounting for 500 000 deaths per year worldwide. Despite a higher prevalence of breast cancer in industrialised than in non-industrialised countries, incidence rates are steadily increasing in less affluent societies.[2] Breast cancer is mainly a postmenopausal disease, with more than three-quarters of tumours hormone responsive. This hormone dependency interacts with environmental and genetic factors to determine incidence and progression of the disease. Lifestyle and environmental effects are potentially modifiable risk factors and offer the prospect of interventions that might ultimately reduce the global burden of the disease.[3] The documented decrease in breast-cancer rates in the USA in 2003, after a gradual rise during the preceding 30 years, exemplifies the effect of risk modification. This reduction has been linked to decreased use of exogenous hormones after adverse reports of an association with increased breast-cancer risk[4] and a possible reduction in the uptake of screening mammography in view of its debatable modest benefit.

Mortality rates for breast cancer have fallen in many industrialised nations since around 1990, having previously been stable or increasing for several consecutive decades.[5–7] These falls in mortality have been attributed mainly to the introduction of mammographic screening programmes and the widespread use of adjuvant systemic therapies with tamoxifen.[8] A US population-based study showed that these mortality trends are accentuated in women with oestrogen-receptor-positive tumours compared with those with hormone-insensitive disease.[9] Moreover, this decrease in mortality was almost exclusively confined to women younger than 70 years (figure 1). This Seminar will focus on the epidemiology, diagnosis, and management of early breast cancer when there is no overt evidence of distant metastases and for which treatment intent is curative. Some patients can be cured with loco-regional treatment alone whereas many will have undetectable micrometastatic disease and require adjuvant systemic therapy.

Epidemiology

Age and female sex are major risk factors for breast cancer, with incidence rates rising rapidly between the ages of 35 and 39 years and subsequently levelling to a plateau after 80 years.[10] Nonetheless, the rate of increase slows around the age of 50 years, corresponding to the average age of menopause, which creates a point of inflection in the age-specific incidence curve known as Clemmesen's hook (figure 2).[11] This transition point is an indicator of the confluence of two separate rate curves for oestrogen-receptor-positive and negative tumours that have fairly favourable and poor prognoses, respectively.[10] The incidence of oestrogen-receptor-negative tumours increases rapidly until age 50 years and then flattens or decreases. By contrast, the incidence of oestrogen-receptor-positive tumours is similar up to the age of 50 years, but then continues to climb at a slower pace.

Search strategy and selection criteria

We searched the Cochrane Library and Medline between 1998, and 2008, with the term "breast cancer". In section of publications, we used discretion from our perception of the importance of the articles on the basis of citation within the medical published work and at major international conferences (San Antonio Breast Cancer Symposia; American Society of Clinical Oncology meetings). We restricted searches to the past 5 years, but some older referenced papers were collated from our personal collections. Some review articles have been cited to provide a more comprehensive list of references than is permissible in this Seminar.

Thus oestrogen-receptor-negative tumours tend to occur earlier in life and oestrogen-receptor-positive tumours are more common in older women. The peak ages of onset for these two tumour phenotypes are 50 and 70 years of age, respectively, and they seem to have different underlying causes and pathobiology. Reproductive and anthropomorphic factors have opposing effects, with nulliparity, obesity, and oral contraceptive use decreasing the risk of early-onset breast cancers while increasing the risk in older women.[12–14]

There are pronounced racial differences in the incidence and mortality of breast cancer.[15] Although age-standardised incidence rates are higher in white women than in those of African-American descent, these rates cross at about age 50 years. At younger ages, breast-cancer incidence rates are higher in African-American women, whereas rates are greater in their white counterparts at 50 years of age and older. Age-adjusted breast-cancer mortality rates were congruent between African-Americans and white Americans until the early 1980s, but thereafter a continued divergence was evident with higher mortality rates for African-American than for white people.[16] These differential mortality rates coincided with the introduction of mammographic screening in conjunction with adjuvant systemic therapy as an integral component of breast-cancer management.[16] Black women have a higher proportion of oestrogen-receptor-negative tumours than do white women and are therefore less likely to receive endocrine treatment. Furthermore, socioeconomic variation leads to inequalities in terms of health-insurance cover and educational attainment, which are likely to restrict access to new treatments and screening programmes for ethnic groups. A combination of intrinsic differences in response and health-care provision might account for the widening racial disparity in breast-cancer mortality rates within the USA.[16,17]

Familial forms of breast cancer incorporate both high and low genetic risk. When several first-degree relatives are affected, clustering is probably hereditary and attributable to high-risk susceptibility genes such as *BRCA1* and *BRCA2*.[18] These are tumour suppressor genes that display an autosomal dominant pattern of inheritance with variable penetrance. Mutations within these two genes account for around three-quarters of hereditary breast cancer cases (5–10% of all breast cancer) and confer a lifetime risk of between 80–85% by age 70 years.[19] Additionally, *BRCA1* mutations are associated with ovarian cancer risk of 20–40%. Within cells, the effects of *BRCA1* and *BRCA2* are recessive, and both copies of an allele must be lost or mutated for cancer

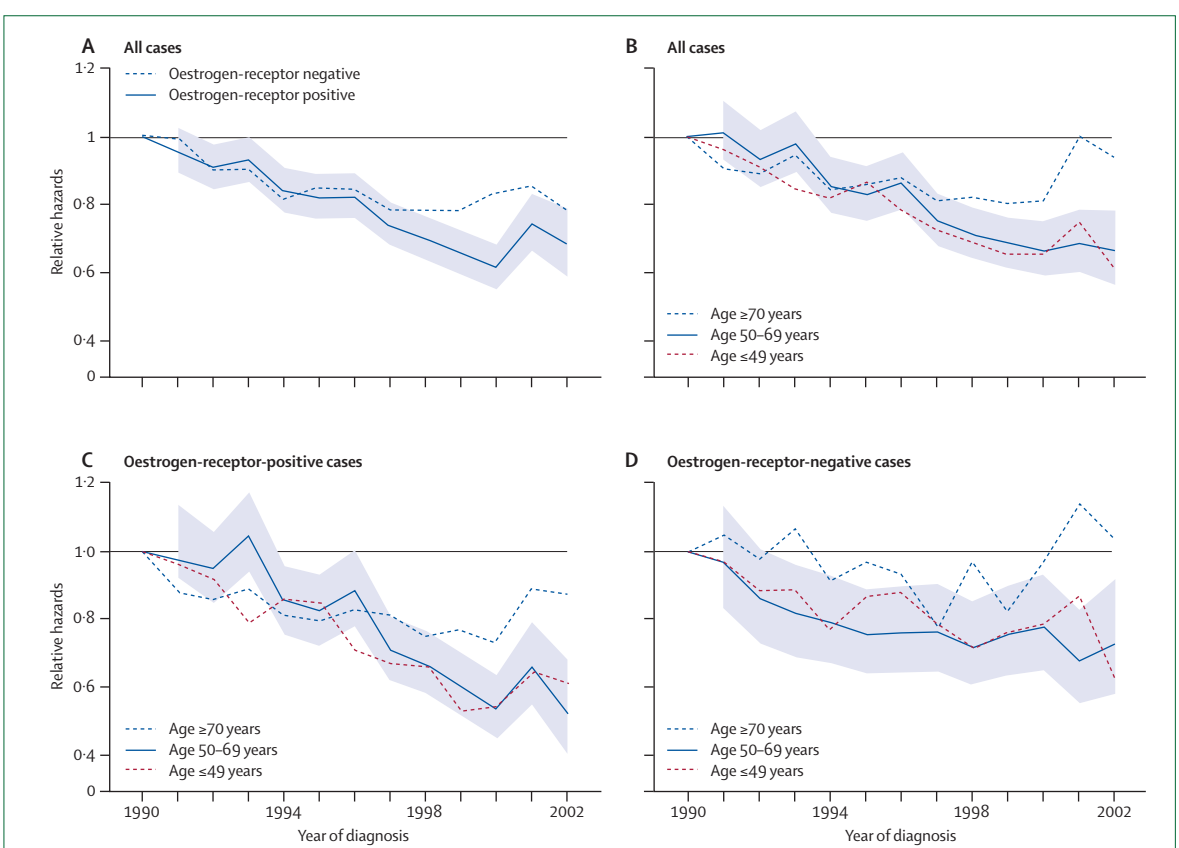

Figure 1: **Relative hazard rates of breast-cancer death according to oestrogen-receptor status and age at diagnosis**
Shading indicates 95% CIs. Reprinted with permission from the *Journal of Clinical Oncology*.[9]

progression. Individuals with a germline mutation in these genes have a dominantly inherited susceptibility, and the second so-called hit occurs in the somatic copy. Tumours from genetically predisposed patients show loss of heterozygosity in the wild-type *BRCA1* allele,[20] but mutations of *BRCA1* and *BRCA2* are uncommon in sporadic breast cancers. Other genes involved in genetic predisposition include *p53* (Li-Fraumeni syndrome), *AT* (ataxia telangiectasia), and *PTEN* (breast and thyroid cancer). Low penetrance genes such as *CHEK* mutations might collectively be responsible for up to 25% of familial cases; although they confer a reduced risk, they are more prevalent within the population.[21]

Breast-cancer risk is modulated by factors affecting the hormonal milieu; most mammary tumours are stimulated by oestrogens, and oestrogen-receptor-negative tumours can evolve from oestrogen-receptor-positive lesions rather than arising de novo. A woman's cumulative lifetime exposure to oestrogen determines the level of this environmental risk. Thus early menarche (<12 years *vs* 16 years) and late menopause (>55 years *vs* <45 years) are associated with relative risk increases of about 1·2.[3] Levels of oestrogen and rates of proliferation in breast epithelium are low after menopause, which when induced iatrogenically at younger than 40 years of age reduces the risk of breast cancer by almost two-thirds.[3] A first full-term pregnancy at younger than 20 years of age is protective for breast cancer, and high circulating concentrations of progesterone can cause terminal differentiation in pluripotential stem cells of immature breast tissue. Nulliparity is a well known risk factor for breast cancer since Ramizzini described *horrendis mammarium canceris* in Catholic nuns.[22] However, women who defer childbearing beyond 35 years of age have an increased relative risk compared with nulliparous women, which might have relevance to contemporary reproductive practices in which late pregnancies are associated with prolonged use of the oral contraceptive pill and a greater chance of pregnancy-related breast cancer.[23]

Hormone-replacement therapy increases the relative risk of breast cancer by roughly 35% after 10 years of use, although cancers developing in women who have ever used this therapy tend to be of more favourable prognosis.[24] Hormone-replacement therapy should be avoided in breast-cancer survivors, and more than doubles the risk of recurrence.[25] Moderately vigorous physical activity of up to 7 h per week can reduce the risk of breast cancer by almost 20%, and this effect is independent of menstrual function. Daily strenuous exercises reduce risk by up to 50% in women aged 14–22 years.[26] Alcohol consumption increases breast-cancer risk irrespective of the type of beverage consumed.[27] High mammographic breast density is a powerful independent predictor of breast-cancer risk and is associated with an increased ratio of glandular to fatty tissue.[28] Only a quarter of sporadic cases of breast cancer have any identifiable risk factor.

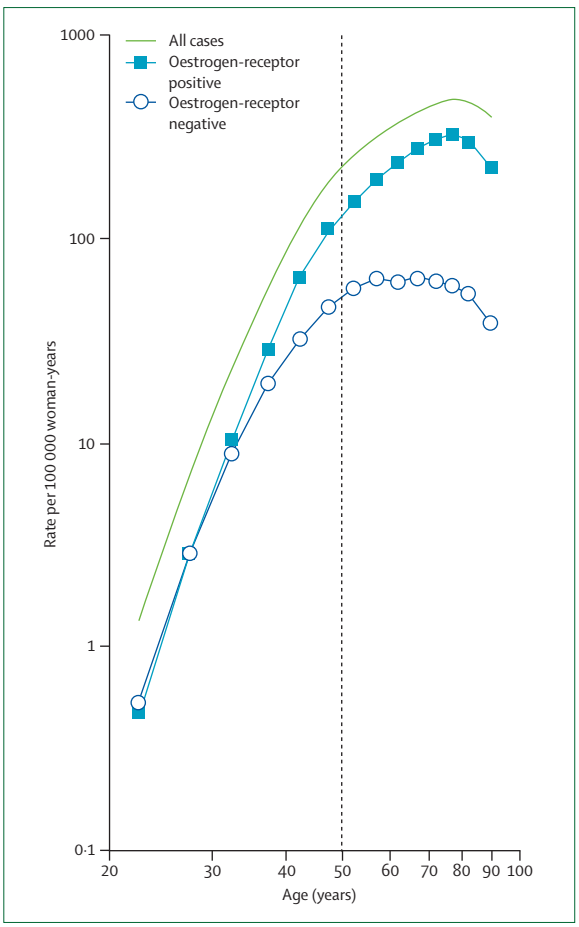

Figure 2: **Age-specific incidence rates (SEER Database) in female patients with breast cancer, showing point of inflexion (Clemmesen's Hook) at around 50 years of age**
SEER=Surveillance, Epidemiology and End Results program of the National Cancer Institute. Reproduced with permission from Springer-Verlag.

Diagnosis

About three-quarters of symptomatic breast cancers will present with a discrete breast lump. However, most patients referred to a breast clinic with a lump will have benign disease, and initial clinical examination will aim to establish whether a dominant mass or localised glandular nodularity is present. The physical characteristics of benign and malignant breast lumps overlap substantially. Thus complete clinical evaluation involves triple assessment, integrating information from clinical examination, radiological imaging, and percutaneous needle biopsy. A diagnostic mammogram can confirm a clinical suspicion of malignancy and typically shows a spiculate opacity or microcalcification. It can sometimes show the extent of malignancy (especially when associated with microcalcification) and identify occult (non-palpable) lesions in the ipsilateral or contralateral breast. Mammography does not show evidence of malignancy in 10% of patients with breast cancer.[29]

Breast ultrasound with 12–15 MHz transducers is complementary to mammography and increases diagnostic accuracy. It provides a measurement of tumour size, correlating well with pathological estimates.[30] Modern ultrasound devices incorporate a Doppler facility and are increasingly being used to image the axillary nodes and deselect patients for sentinel-lymph-node biopsy. Tissue diagnosis is essential and can be obtained with either fine-needle aspiration cytology or core biopsy. Before image-guided biopsy techniques, most tissue acquisition involved open excision or incision biopsy. Percutaneous needle-biopsy techniques can now provide a definitive diagnosis for most benign and malignant diseases.[31] Although fine-needle aspiration cytology simply, quickly, and cost-effectively establishes tissue diagnosis, it has lower sensitivity and specificity than does core biopsy.[31] Despite false-negative results with both, core biopsy with wide-bore needle is preferred to fine-needle aspiration cytology and yields solid cores of tissue that maintain tissue architecture and allow distinction between invasive and non-invasive carcinoma.[32] Biopsy samples of mass lesions can be taken with ultrasound or stereotactic guidance, whereas microcalcification usually mandates stereotactic methods.[33] The standard core-biopsy needle is either 14 or 16 gauge, but larger volumes of tissue can be obtained from vacuum-assisted core biopsy devices with a range of needle sizes, but most often an 11 gauge needle. Vacuum-assisted core-biopsy devices reduce the chance of underdiagnosis and increase the chance of obtaining a definitive preoperative diagnosis, allowing appropriate planning of breast-cancer surgery.[34]

When clinical examination, radiology, and core biopsy or fine-needle aspiration cytology show benign features only, the probability of malignancy is very low. A diagnostic (surgical) excision biopsy is warranted in the absence of concordance, although repeat core-needle biopsy can be attempted. MRI is used selectively in the diagnostic workup of breast-cancer patients to clarify the extent of a lesion and establish whether satellite foci are present in patients otherwise amenable to breast-conservation surgery.[35] However, evidence suggests that patients assessed with MRI are more likely to undergo (unnecessary) mastectomy instead of breast-conservation surgery.[36,37] Rates of ipsilateral breast tumour recurrence (IBTR) are fairly low—at 8 years rates are similar in patients receiving breast-conservation surgery with (3%) and without (4%) preoperative MRI imaging[38]—and additional lesions detected by MRI might not be clinically relevant or might be adequately treated with adjuvant therapies.[39]

A substantial proportion of breast cancers in the USA and western Europe are detected with screening mammography. Randomised controlled trials have confirmed that screening mammography with or without clinical breast examination in postmenopausal women reduces breast-cancer mortality by about 20%.[40] The use of screening mammography in premenopausal women remains controversial, and is probably not cost effective.[41] Some suggest that clinical breast examination should accompany mammographic screening, since some cancers are radiologically occult but clinically palpable.[42] Breast self-examination has not yet proven beneficial in clinical trials.[43] Breast MRI screening has been recommended for high-risk women with *BRCA1/2* mutation carriage.[44] The sensitivity of breast MRI and cancer-detection rates within this group are better than with mammography; however, data from prospective randomised controlled trials assessing the effect on breast-cancer mortality are scarce.

Biological hypotheses

Two biological notions of tumour pathogenesis have guided strategies for loco-regional and systemic treatment of breast cancer.[45] According to the Halstedian paradigm, breast cancer is a localised disease at inception with progressive and sequential spread from local tissues to lymph nodes and in turn haematogenous dissemination. IBTR is considered a cause of distant metastases, with the chance of cure related to the extent of primary loco-regional treatment. The Fisherian paradigm presupposes that breast cancer is predominantly a systemic disease at the outset, with cancer cells entering the bloodstream at an early stage of tumour development. Circulating tumour cells might be destroyed by the immune system, but some will establish viable micrometastatic foci at distant sites. Micrometastases at the time of diagnosis will determine a patient's clinical fate. IBTR is regarded as an indicator of distant-relapse risk and indicates a host-tumour relation that favours development of distant disease or activation of processes leading to a kick start of micrometastases. This notion of biological predeterminism has dominated approaches to breast-cancer management over the past three decades and emphasised the importance of systemic therapies targeting distant micrometastatic disease. Long-term follow-up of the largest breast conservation trial (NSABP B-06) at 20 years suggests that variations in extent of loco-regional treatments do not affect overall survival,[46] supporting the idea that local recurrence is an indicator of risk for development of distant disease that reflects intrinsic biology of the tumour.[47] Several studies have shown that IBTR is the strongest independent predictor of distant relapse, conferring an increased risk of up to three-fold to four-fold.[48] Although IBTR contributes roughly a third to the overall recurrence risk (Blamey R, University of Nottingham, personal communication), whether IBTR is causally related to distant relapse or merely associated with survival is unknown.

In a meta-analysis by the Early Breast Cancer Trialists' Collaborative Group (EBCTCG), local radiation treatment to either the breast after breast-conservation surgery or the chest wall after mastectomy showed an overall survival benefit at 15 years.[49] For treatment comparisons in which the difference in local recurrence rates at 5 years was less than 10%, survival was unaffected. When

differences in local relapse were substantial (>10%), moderate reductions in breast-cancer-specific and overall mortality were recorded. Absolute reductions were 19% for local recurrence at 5 years and 5% for breast-cancer mortality at 15 years, representing one life saved for every four loco-regional recurrences prevented by radiotherapy at 5 years. This analysis showed conclusively that differences in loco-regional treatments that substantially improve rates of local control will affect long-term survival of patients with breast cancer. Local control does matter and rates of local recurrence should be kept to a minimum in the first 5 years. Up to a quarter of local recurrences will be a determinant and not simply an indicator of risk for distant relapse and death.

Molecular profiling can help to predict the biological behaviour and pattern of spread for individual tumours and avoid undertreatment and overtreatment with both loco-regional and systemic therapies.[50] Malignant stem cells are either quiescent or cycle fairly slowly, and are resistant to conventional chemotherapy. Their ability to self-renew provides the opportunity for regeneration and clinical recurrence of cancer. Identification of biochemical pathways that are unique to cancer stem cells will allow selective targeting of this important subpopulation of tumour cells. Cellular response to therapies should be anticipated and escape mechanisms co-targeted.

Surgery

The introduction of conservative surgery for breast cancer coincided with reduced tumour size at presentation and a shift in the underlying biological hypothesis. Breast-conservation surgery is now an established procedure and the preferred standard of care for management of women with early-stage breast cancer. Instigation of widespread mammographic screening has contributed to a stage shift for newly diagnosed disease, with an average tumour size at presentation of less than 2 cm. At least two-thirds of patients are eligible for breast-conservation surgery, but rates of mastectomy vary both geographically and institutionally.[51] Selection of patients for this surgery is crucial, with an inverse relation between competing oncological demands for surgical radicality and cosmesis. A balance exists between the risk of IBTR and cosmetic results, with oncoplastic surgery advancing the limits of surgical resection.

Two factors emerge as principal determinants of true local recurrence within the conserved breast: margin status and the presence or absence of an extensive in-situ component. Lymphatic invasion and young age (<35 years) are primary predictors for increased risk of IBTR. Consistent associations have been recorded for larger tumour size (>2 cm) and higher histological grade but not for tumour subtype or nodal status.[52] Results of the EBCTCG overview have reinforced the link between local control and mortality, leading to an emphasis on adequacy of surgical excision and other treatment-related variables such as radiotherapy.[49] Attainment of gross macroscopic clearance of the tumour at operation is no longer acceptable; all radial margins should be clear of tumour microscopically. A positive resection margin has not been uniformly defined, which has compounded issues relating to microscopically negative margins and degrees of surgical clearance—eg, how wide must a negative margin be to result in acceptable rates of local recurrence (1–2% per year)? Many surgeons regard a margin clearance of 2–3 mm to be appropriate, although up to 45% of American radiation oncologists consider a margin as negative provided that no tumour cells are at the inked edge.[53] Others strive for a radial margin clearance of 5 mm, which can lead to re-excision rates of up to 50% but is associated with very low rates of IBTR. Detection of further tumour is unusual when re-excision is done to achieve a wider margin rather than a negative margin. Singletary[54] has provided a useful analysis, showing median rates of IBTR of 3%, 6%, and 2% when margins of clearance were 1 mm, 2 mm, or just clear, respectively. Thus although rates of recurrence are determined by negative margin status, no direct relation exists between margin width and rates of local recurrence. When the first re-excision fails to achieve surgical clearance, mastectomy is often indicated and becomes necessary if margins remain positive after a reasonable number of surgical attempts (up to three).[55]

Practices are consistent with the notion that IBTR develops from re-growth of residual cancer cells in peritumoral tissue. Moreover, the invasive element confers the increased risk of distant failure; when local recurrence is exclusively ductal carcinoma in situ, features of the original primary tumour will determine systemic risk.

Most patients considered suitable for breast-conservation surgery will have a unifocal tumour measuring 3 cm or less and lying more than 2 cm from the nipple areolar complex. These patients usually have a favourable ratio of tumour to breast size and are amenable to conventional forms of wide local excision in which the tumour is excised with a roughly 2 cm margin of surrounding breast tissue without the need for any formal breast remodelling. Although a re-excision might be needed in up to a quarter of cases to achieve microscopically clear radial margins, an optimum cosmetic result should be attained after irradiation of the remaining breast tissue. Notwithstanding attempts at breast-conservation surgery, mastectomy is clearly indicated for some patients on the basis of tumour size or location, multifocality, an inflammatory component, or patient choice. Achievement of a good cosmetic outcome becomes progressively more difficult as the proportion of breast tissue removed increases. Although the absolute volume of tissue excised is surgeon dependent, a greater percentage is associated with larger tumours. When more than 10–20% of breast volume is removed, results might be unsatisfactory cosmetically.[56] Partial-breast reconstruction with oncoplastic procedures often allow wide resection of tissue, increasing the chance of tumour-free margins. Despite these techniques

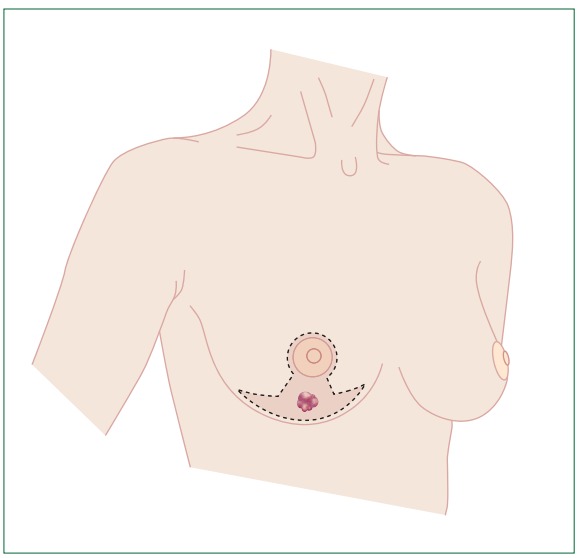

Figure 3: **A tumour in the inferior quadrant of the breast can be excised as part of a reduction mammoplasty specimen with wide surgical margins**

providing an opportunity for enhancing quality of life by improving cosmetic outcome and psychological well-being,[57] there are no long-term follow-up data to substantiate the claim for reduced rates of local relapse. Moreover, transposition of glandular tissue could jeopardise accurate targeting of any radiotherapy boost, unless it is given intraoperatively. Therapeutic mammoplasty can potentially improve cosmetic outcome when tumour size or location would otherwise lead to sub-optimum cosmesis after conventional breast-conservation surgery (figure 3).[58] Strict oncological selection criteria should still be applied;[59] when the estimated risk for IBTR is high, despite clear margins and a good cosmetic result, mastectomy with immediate breast reconstruction should be offered. The development of oncoplastic surgery and partial-breast reconstruction has improved the application of breast-conservation surgery to management of breast cancer, but careful patient selection is crucial. Often a contralateral procedure is required for symmetrisation, particularly when volume displacement rather than replacement techniques are used.[60]

Most patients who are healthy and younger than 70 years with a non-inflammatory or locally advanced tumour should be offered immediate breast reconstruction together with a skin-sparing mastectomy in which the nipple areolar complex is removed but much of the breast skin envelope remains. Skin-sparing mastectomy represents the latest phase in development of less mutilating forms of mastectomy and has revolutionised results of immediate breast reconstruction by preserving the inframammary fold and avoiding the need for resculpturing of any imported skin or tissue expansion of residual chest-wall skin. No evidence suggests increased rates of local recurrence with skin-sparing mastectomy, and the precise skin incision should be tailored to the individual patient with removal of any involved skin overlying a tumour.[61] Breast volume can be reconstituted with a variety of techniques including subpectoral tissue expander, extended autologous latissimus-dorsi flap, implant-assisted latissimus-dorsi flap, or a free/pedicled transverse rectus abdominus flap. Judicious patient selection and joint decision-making will help keep any disparity between patient expectation and clinical reality to a minimum and maximise satisfaction.

Many women now receive postmastectomy radiotherapy.[49,62,63] Anticipation of chest-wall irradiation will affect the choice of reconstructive technique; an implant-only reconstruction is generally avoided when postmastectomy radiotherapy is a possibility.[64] The potential problems of capsular contracture in this group of patients with implant-based reconstruction have led to a modified surgical approach with a delayed immediate reconstruction. A skin-sparing mastectomy can be undertaken initially with placement of a temporary tissue expander that acts as scaffolding for the skin flaps. Chest-wall irradiation can then be given and definitive reconstruction undertaken later. The viability of the native mastectomy flaps after radiation causes concern, and it might be preferable to proceed with immediate reconstruction with a latissimus-dorsi flap and implant for all patients and undertake implant exchange if and when required. An extended autologous latissimus-dorsi flap is not necessarily more tolerant of radiotherapy, and substantial donor-site morbidity occurs. However, delayed immediate reconstruction is a method that can potentially preserve the aesthetic benefits of immediate breast reconstruction with preservation of the three-dimensional skin envelope and more accurate targeting of tangential radiotherapy beams.

Methods for accurately staging the axilla continue to evolve, but remain dominated by sentinel-lymph-node biopsy, which is now widely practised and accepted as a standard of care. Dual labelling techniques with blue dye and isotope are associated with a shorter learning curve and optimum performance indicators such as rates of identification (>90%) and false negativity (5–10%).[65] Blue dye-assisted node sampling removes three to four blue and palpably suspicious nodes and can be a pragmatic and cost-effective method when radioisotope facilities are unavailable.[66] However, this method is associated with a higher false negative rate and lacks the reassurance provided by the absence of any residual radioactivity within the axilla. Results from the largest sentinel lymph node biopsy trial show an overall false negative rate of 9·8%, with higher rates when only one sentinel node is removed rather than two to three nodes.[67] Completion axillary-lymph-node dissection is recommended for all patients with either micrometastatic or macrometastatic deposits in the sentinel lymph node.[65] The chance of non-sentinel lymph-node involvement is related to the volume of disease in the sentinel node, but nomograms devised for estimation of this involvement are difficult to

reliably apply in practice and are less accurate when the predicted incidence of non-sentinel lymph-node positivity is low.[68] For some patients, the risk to benefit ratio for detection of positive cases of non-sentinel lymph nodes might not justify any delayed procedure. Low rates of axillary relapse are unlikely to translate into any meaningful reduction in long-term survival in an older group of patients with smaller non-high-grade tumours.[69] Methods for intraoperative assessment of sentinel lymph nodes obviate the need for a delayed axillary-lymph-node dissection, but detection of micrometastases with either touch imprint cytology or frozen section is problematic. New techniques based on reverse-transcriptase PCR can potentially overcome difficulties of limited node sampling and operating parameters set at a threshold for detection of metastases greater than 0·2 mm in size but not isolated tumour cells (≤0·2 mm).[70] Real-time PCR might allow quantitation and differentiation between macrometastases and micrometastases.

Rates of clinical regional recurrence in patients with negative sentinel-lymph-node biopsy who have not proceeded to axillary-lymph-node dissection range from 0 to 1·4%, with fairly short follow-up of 3 years or less.[71] Any residual disease within the axillary nodes will be low volume, and longer follow-up might be needed for any clinical manifestation of regional recurrence. Kujit and Roumen[72] report an actuarial rate of 5% at a median follow-up of 6·5 years, predicting that up to 10% of patients might eventually develop isolated axillary recurrence after a negative sentinel-lymph-node biopsy.

Radiotherapy

Long-term follow-up of breast-conservation trials confirm significantly increased rates of local relapse when radiotherapy is omitted.[46,73] However, rates of IBTR are acceptable when breast-conservation surgery is combined with whole-breast irradiation, usually delivered via conventional tangential breast fields at a total dose of 46–50 Gy in 25 fractions over 5 weeks with an optional booster dose (10–20 Gy). Within the NSABP B-06 trial, 39·2% of patients undergoing wide local excision only had developed local recurrence at 20 years' follow-up compared with 14·3% for those receiving radiotherapy after lumpectomy ($p<0·001$).[46] Moreover, cosmetic results are satisfactory when neither the volume of breast tissue excised or the radiation fraction size are excessive.[56] A group of patients for whom rates of IBTR are not further reduced by radiotherapy compared with observation or tamoxifen therapy alone has not been defined.[74–76] Omission of radiotherapy should be cautioned at present since it can lead to rates of IBTR approaching 30% for small tumours of favourable grade, and local control does affect overall survival.[49] Older women benefit in terms of breast-cancer-specific survival from radiotherapy after breast-conservation surgery, and tamoxifen alone cannot substitute for radiotherapy. Comorbidities can otherwise reduce life expectancy for some older women for whom any additional local control (3–6% risk absolute reduction) from radiotherapy might not be clinically significant.[77,78]

A group of techniques has been developed—accelerated partial-breast irradiation—that decrease the volume of breast tissue irradiated and the duration of treatment. More than three-quarters of true breast recurrences occur at the site of lumpectomy, and whole-breast irradiation might be unnecessary. These techniques are focused on the tumour bed and a zone of surrounding tissue of variable depth. The advent of CT-based treatment planning kept exposure of normal tissues to a minimum and helped radiotherapists cope with the challenges resulting from the peculiar shape of the breast and contiguity of important surrounding structures (eg, heart and lungs). Computer technology assisted with placement of multiplanar interstitial catheter implants for brachytherapy after lumpectomy. Treatment was aimed at the tumour bed and a margin of tissue to a depth of 1–2 cm. This technique allowed radiotherapy (34 Gy) to be completed within 1 week rather than 5 or 6 weeks. Single institution series with more than 5 years of follow-up show rates of local control to be similar to whole-breast irradiation for matched and appropriately selected subsets of patients.[79–81] Despite a US multicentre trial confirming reproducibility of these favourable results across institutions, the perceived complexity of brachytherapy detracted from its popularity and it remains available in only a few centres worldwide.[82]

Two further techniques of accelerated partial-breast irradiation have been pioneered: intraoperative radiotherapy and MammoSite. Intraoperative radiotherapy delivers a high dose of radiation as one fraction at the time of surgery, allowing precise application of radiation dose to the target area to eliminate tumour foci around the surgical bed. It potentially intensifies the tumour kill effect of surgery and radiotherapy, although some are concerned about the radiobiological equivalence of one dose of intraoperative radiotherapy (21 Gy) compared with conventional whole-breast irradiation. This concern applies particularly to the low-energy X-ray source (50 kV) used in the TARGIT trial[83] compared with electron beam therapy (electron intraoperative therapy)[84] for which depth of penetration is restricted. However, mathematical and laboratory models suggest that TARGIT might be better than conventional therapy,[85,86] and initial clinical results are encouraging.[83] Intraoperative radiotherapy facilitates an integrated approach to the multidisciplinary treatment of cancer, but requires specialised equipment and for electron intraoperative therapy a dedicated suite. An alternative technique of brachytherapy is given via a double lumen balloon catheter (MammoSite) placed within the surgical cavity.[87] This device delivers a total dose of 34 Gy in ten fractions (via a high-dose rate remote afterloader) and is now a common method of accelerated partial-breast irradiation, using equipment already present in many centres. Preliminary results with 5 years' follow-up show low rates of local recurrence (0–6%) and good to excellent cosmetic results in 80% of patients.[88,89]

Three-dimesional conformal radiotherapy is a form of accelerated partial-breast irradiation that uses an external beam to treat smaller volumes than whole-breast irradiation does. Despite being non-invasive, achieving high levels of conformality is difficult.[90,91] The related technique of intensity-modulated radiotherapy delivers conformal dose distributions and improves homogeneity.[92] The combined NSABP B-39/RTOG 0413 trial incorporates three techniques for accelerated partial-breast irradiation (three-dimensional conformal, interstitial brachytherapy, and MammoSite) and aims to assess these techniques in comparison with whole-breast irradiation with primary endpoints of local recurrence, disease-free survival, and overall survival.[93] The START trial has assessed accelerated hypofractionated whole-breast irradiation and showed that patients given a lower overall radiotherapy dose in fewer, larger fractions have similar local control and fewer adverse side-effects than does a dose of 50 Gy in a standard 5-week schedule. This finding supports hypofractionation as a safe and effective approach, but long-term follow-up is required to assess local control and late toxic effects.[94]

Radiotherapy after mastectomy encompasses irradiation of the chest wall and skin together with regional lymph nodes. The indications for this treatment continue to evolve, but all trials have shown that it reduces the proportional risk of local failure by two-thirds to three-quarters of patients, including those with tumours larger than 5 cm and four or more positive axillary lymph nodes. However, data for the benefit of postmastectomy radiotherapy in terms of overall survival are conflicting; an overview by the EBCTCG confirms that postmastectomy radiotherapy in node-positive women results in an absolute survival gain at 15 years.[49] Although postmastectomy radiotherapy reduced rates of local relapse in node-negative patients, mortality was not reduced. In the Danish and British Columbia trials of postmastectomy radiotherapy in premenopausal node-positive women receiving chemotherapy,[61,62] the proportional survival benefits were similar for patients with one to three and four or more positive nodes. However, some aspects of trial design were controversial and any survival advantage within the intermediate-risk groups (one–three nodes positive) could be masked by toxic effects from the radiotherapy. New radiation techniques using tangential fields minimise cardiotoxicity, as do methods such as intensity-modulated radiotherapy.[95] The SUPREMO trial is assessing whether modern chemotherapy regimens and postmastectomy radiotherapy can lead to overall-survival improvements in this intermediate-risk group.[96]

Adjuvant systemic therapies

Incorporation of adjuvant systemic therapies into the multidisciplinary management of breast cancer has led to improvements in rates of disease-free and overall survival.[97,98] The indication for adjuvant systemic therapy after definitive surgery is based on established prognostic factors, including age, comorbidities, axillary-lymph-node involvement, tumour size, and tumour grade.[99] In addition to these well established clinicopathological factors, molecular tests can assess the estimated risk of recurrence in patients with early-stage breast cancer and identify distinct biological classes of tumour. Three prognostic tests have been approved for clinical application in the USA:[100] Oncotype DX, MammaPrint, and H/I, which are based on a 21-gene profile, a 70-gene profile, and expression of the *HOXB13/IL17BR* genes, respectively. The Oncotype DX and *HOXB13-IL17BR* assays measure gene expression with reverse-transcriptase PCR and the MammaPrint assay uses complementary DNA microarray technology. One of the advantages of reverse-transcriptase PCR is that gene expression can be measured in formalin-fixed paraffin-embedded tumour tissue, whereas the microarrays need fresh frozen tissue. Although prognostic tests provide information about risk of recurrence and death, predictive markers are needed to select the optimum therapy for individual patients. The best characterised molecular predictive markers are the oestrogen receptor, the progesterone receptor, and the human epidermal growth factor receptor 2 (HER2).[101]

The responsiveness of breast tumours to hormonal manipulation provides a unique therapeutic opportunity in the form of targeted treatment. The antioestrogen tamoxifen confers a proportional reduction in mortality of 26% and up to 47% reduction in local recurrence at 10 years' follow up, with benefit confined to oestrogen-receptor-positive tumours.[98] Tamoxifen is effective in both premenopausal and postmenopausal women, although premenopausal women are eligible for ovarian suppression with either luteinising hormone-releasing hormone analogues or laparoscopic oophorectomy when disease is hormone responsive.[102] An advantage of luteinising hormone-releasing hormone agonists is their potentially reversible effects on cessation of treatment. Whether ovarian suppression can provide an alternative to chemotherapy in patients with oestrogen-receptor-positive disease, and whether luteinising hormone-releasing hormone agonists confer any additional benefit when combined with standard treatments, is being investigated.

The aromatase inhibitors represent an important advance in endocrine therapy of breast cancer. The oral agents anastrozole, letrozole, and exemestane are of comparable antitumour efficacy and are potentially interchangeable, although long-term data for side-effect profiles must be obtained before definitive pronouncements on clinical use. The American Society of Clinical Oncology Technology Assessment recommends that adjuvant hormonal therapy for postmenopausal women should include an aromatase inhibitor prescribed either as initial therapy or sequenced after tamoxifen for 2–3 years' (early switch) or 5 years' duration.[103] The largest study of adjuvant aromatase inhibitors showed a continuing divergence of the curves for disease-free survival at 68 months' follow-up, with evidence of a

carry-over effect and a reduction in time to distant recurrence favouring anastrozole.[104] The absolute benefit for time to recurrence has increased from 2·8% at 5 years to 4·8% at 100 months. This head-to-head comparison of tamoxifen versus anastrozole shows no difference in overall survival, although there is a non-significant trend for improved breast-cancer-specific survival in the latest analysis.[105] The fairly good prognostic parameters might ultimately obscure translation into a significant benefit for this endpoint.[104,106]

The IES trial is the only adjuvant study to show an overall-survival advantage for use of an aromatase inhibitor within the conventional 5-year treatment span.[107] These results, together with a meta-analysis of the Austrian (ABCSG 8/ARNO 95) and Italian (ITA) studies, support early sequencing with a switch to an aromatase inhibitor after 2–3 years of tamoxifen[108] as an efficacious approach, with improvement in overall survival for oestrogen-receptor-positive patients. The proportional risk reductions for disease-free survival are greater within the early switch than in head-to-head comparisons of tamoxifen and an aromatase inhibitor. Although interim results of the BIG 1-98 study[109] showed a disease-free survival benefit for 5 years of letrozole compared with 5 years of tamoxifen, definitive results of this study have not shown a clear advantage from an early switch policy in terms of recurrence rates compared with 5 years of an aromatase inhibitor.[110] At a median follow-up of 72 months, there was no significant difference in disease-free survival for 5 years of letrozole compared with either of the switch groups. However, pair-wise comparisons suggested a minor benefit for letrozole (5 years) compared with tamoxifen for 2 years followed by letrozole for 3 years. The inverse sequence of tamoxifen after 2 years of letrozole was equivalent to monotherapy, and patient cross-over from tamoxifen to letrozole precluded any updated comparison of the monotherapy groups.

On the basis of these data, some authorities recommend that patients at greatest risk of relapse might benefit most from an upfront aromatase inhibitor, whereas those with lower hazard rates for relapse might be best treated with an early-switch regimen involving tamoxifen for 2–3 years followed by an aromatase inhibitor for a total duration of 5 years. Although results of the BIG 1-98 study show greatest benefit from aromatase inhibitors for node-positive patients, the converse is true for the ATAC study.[105] Moreover, high-grade tumours derive no additional benefit from upfront aromatase inhibitors, and no conclusive evidence supports HER2 status as being predictive of response to aromatase inhibitors. Benefits in terms of disease-free and overall survival must be balanced against long-term adverse effects on bone health, cognitive function, and cost. Some patients at very low risk of relapse might derive minimal additional benefit from incorporation of an aromatase inhibitor into their treatment schedule and should receive tamoxifen only. Breast-cancer patients remain at chronic risk of relapse, and aromatase inhibitors offer the opportunity for extended adjuvant therapy beyond 5 years with use of an agent with a different mechanism of action. In the MA-17 trial of extended adjuvant treatment,[111] letrozole therapy significantly improved disease-free survival compared with placebo after completion of 5-years' standard tamoxifen treatment in node-positive patients.

Adjuvant chemotherapy improves rates of disease-free and overall survival for patients with early-stage breast cancer irrespective of nodal status.[112] US guidelines recommend adjuvant chemotherapy for healthy patients with axillary-node involvement and for node-negative disease when tumours are larger than 1 cm or in the presence of other adverse prognosticators (eg, age <35 years, negative oestrogen-receptor or progesterone-receptor status, high-grade tumour).[113] All patients within a subgroup are assumed to derive similar benefit from chemotherapy, but many are overtreated and do not have micrometastatic disease at presentation. Identification of patients with distant microscopic spread is particularly relevant in patients with node-negative, oestrogen-receptor

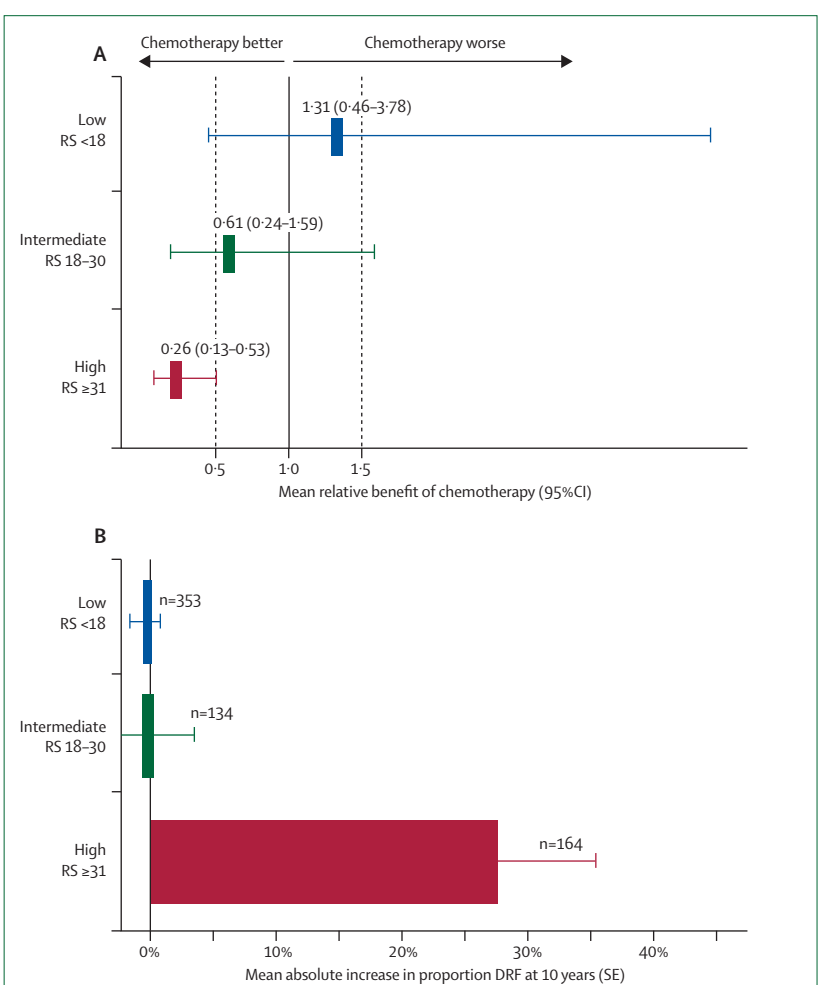

Figure 4: **Relative (A) and absolute (B) benefit of chemotherapy as a function of recurrence-score (RS) risk category in low, intermediate, and high RS groups**
DRF=distant recurrence free. Reprinted with permission from *Journal of Clinical Oncology*.[115]

or progesterone-receptor-positive breast cancer. Adjuvant endocrine therapy is highly effective in such cases and the contribution of chemotherapy not well defined. The prognostic and predictive roles of the Oncotype DX assay were assessed in archival tissue from treated node-negative, oestrogen-receptor-positive tumours. Tamoxifen was most effective when the recurrence score was low (≤18),[114] whereas patients whose primary tumours had a high (≥31) recurrence score derived more benefit from adjuvant chemotherapy (figure 4).

The 21-gene assay was also predictive of benefit from adjuvant chemotherapy in patients with node-positive breast cancer. A US trial randomly assigned premenopausal women with node-positive, oestrogen-receptor-positive breast cancer to tamoxifen or cyclophosphamide, doxorubicin, and fluorouracil (CAF) before or concurrently with tamoxifen. The sequential use of CAF followed by tamoxifen maximised rates of disease-free survival. However, when the Oncotype DX assay was applied to archival primary tissue, only patients with a high recurrence score benefited from CAF chemotherapy.[116] If prospective clinical trials confirm these data, we might be able to spare patients with low-risk breast cancer from undergoing chemotherapy, irrespective of the size of their primary tumours and degree of nodal involvement. Prognostic and predictive values of these molecular assays are based on retrospective subset analyses;[117] TAILORx is a prospective trial that randomises patients with oestrogen-receptor-positive node-negative breast cancer with an intermediate recurrence score (11–25) to chemotherapy and hormonal therapy, or hormonal therapy alone.[118]

The anthracyclines and taxanes are considered the most effective chemotherapies in the adjuvant setting. The taxanes (paclitaxel and docetaxel) have non-cross resistance with conventional agents, and their mechanism of action is to stabilise and prevent disaggregation of microtubules with disruption of the mitotic spindle. A randomised trial showed that four cycles of doxorubicin/cyclophosphamide (AC) followed by four cycles of paclitaxel improves survival compared with AC alone in patients with node-positive breast cancer.[119] Furthermore, giving AC and paclitaxel every 2 weeks (so-called dose-dense approach) improves disease-free survival compared with administration every 3 weeks.[120] Two trials investigating the efficacy of docetaxel in node-positive patients using more intensive anthracycline regimens noted significant improvements in overall survival for taxane-containing regimens.[115,121] A large trial randomised patients with node-positive breast cancer to four cycles of AC followed by either paclitaxel every 3 weeks, weekly paclitaxel, docetaxel every 3 weeks, or weekly docetaxel. Results showed that four cycles of AC followed by one dose of paclitaxel every week for 12 weeks improved overall survival.[122] Whether six or eight cycles are best, or four are sufficient, is unclear. Efforts are ongoing to identify gene-expression profiles that would help select patients for specific chemotherapies.[123] A popular combination is 5-fluorouracil, epirubicin, cyclophosphamide (FEC)-docetaxel for patients with involvement of four or more nodes. Provisional results from the TACT I trial suggest that adding four cycles of docetaxel to one of two standard regimens containing antracycline for unselected patients has little benefit.[124] Retrospective studies indicate that aberrant HER2 expression could correlate with benefit from paclitaxel in the adjuvant setting[125] and that modulation of topoisomerase II gene expression due to deletion or amplification might predict response to anthracycline-based chemotherapy.[126] Co-amplification of HER2 and the topoisomerase II amplicon is associated with increased response rates to anthracyclines.[126]

Trastuzumab (Herceptin) is a monoclonal antibody directed against the extracellular domain of HER2—a tyrosine kinase involved in cell growth and proliferation. Amplification of the *HER2* gene or otherwise overexpression of the cell-surface protein has been associated with a poor prognosis.[127] The HER2 status of the primary tumour or metastatic deposit should be assessed in all patients with breast cancer with either immunohistochemistry, fluorescence in-situ hybridisation, or chromogenic in-situ hybridisation.[128] If the tumour is HER2 positive, the patient is a good candidate for trastuzumab and for participation in clinical trials of novel HER2-directed treatments.

In patients with HER2-positive early-stage breast cancer, trastuzumab improves rates of disease-free and overall survival independent of age, axillary node metastases, and oestrogen-receptor or progesterone-receptor status.[129–131] Two US trials reported a significant reduction in risk of recurrence of about 50% and showed an early survival benefit favouring trastuzumab at 2 years (p=0·015).[129] The European trial (HERA) showed similar reductions in risk of recurrence but no overall-survival advantage.[130] Within the US trials, trastuzumab was given concurrently with an anthracycline-based chemotherapy (AC followed by paclitaxel/trastuzumab) and thereafter continued as single agent therapy for 52 weeks; however, Herceptin was prescribed only after completion of all chemotherapy (any regimen of ≥four cycles) in the European trial. A further international study (BCIRG 006) showed significant improvement in disease-free and overall survival for the non-anthracycline regimen TCH (docetaxel, carboplatin, and trastuzumab) compared with AC-T (doxorubicin/cyclophosphamide followed by docetaxel) and five-fold lower cardiotoxicity than with AC followed by docetaxel/trastuzumab (AC-TH).[131] The risk of cardiac toxicity in the adjuvant setting ranges from 0·5% to 4%.[132] Patients should undergo a baseline echocardiogram or cardiac scan to assess left ventricular ejection fraction before initiation of trastuzumab-based therapy. Serial assessments of left ventricular ejection fraction are recommended every 3 months while receiving trastuzumab with close follow-up in the first 2 years after

completion of treatment. In the event of cardiac toxicity, trastuzumab should be discontinued and left ventricular ejection fraction re-assessed in 4 weeks, although this decision should be made on an individual basis and consider recurrence risk and pre-existing cardiac morbidity.

Lapatinib (Tykerb) is a reversible small-molecule tyrosine-kinase inhibitor directed against epidermal growth factor receptor and HER2.[133] The combination of lapatinib and capecitabine improved rates of disease-free survival compared with capecitabine alone in heavily pretreated patients with metastatic breast cancer.[134] Inhibition of the HER2 kinase seems an important target for this type of molecule, because agents that target the epidermal growth factor receptor kinase selectively (eg, gefitinib and erlotinib) have shown insufficient efficacy in unselected patients with metastatic breast cancer.

Pertuzumab is a monoclonal antibody directed against HER2 that prevents formation of heterodimers between HER2 and other members of the HER family.[135] The binding sites of trastuzumab and pertuzumab localise to different domains of the HER2 protein. Preclinical studies showed a synergistic interaction between pertuzumab and trastuzumab, which is being explored.[135] Overexpression of insulin-like growth factor 1 receptor (IGF-IR) is associated with a poor prognosis and resistance to several drugs, including endocrine therapy and trastuzumab.[136] Approaches to inhibit IGF-IR include the use of monoclonal antibodies, small-molecule tyrosine-kinase inhibitors, and IGF binding proteins. Intracellular transduction pathways activated by growth factor receptors such as HER2 and IGF-IR are potential therapeutic targets, and the mitogen-activated protein kinase (MAPK) and the PI3K/Akt/mTOR pathways have been well characterised in breast-cancer cells.[137] Clinical trials are testing several inhibitors directed against different aspects of these signalling pathways. Postreceptor signalling pathways are not linear but form complex networks with much crosstalk. Multiple compensatory mechanisms exist with some functional redundancy, and blocking one protein (eg, mTOR) often leads to activation of more proximal steps (eg, Akt) and potentially increased proliferation.[137] An approach for overcoming the compensatory loops is to use a combination of inhibitors and to target central signalling nodes that are crucial for sustained growth-inhibitory effects. Novel approaches target not only the cancer cells but also the tumour microenvironment and new vessel formation. Preclinical and clinical studies have shown that blocking angiogenesis improves the efficacy of cytotoxic chemotherapy. Bevacizumab is a recombinant, humanised monoclonal antibody to vascular endothelial growth factor. A phase II trial of trastuzumab and bevacizumab showed that this combination was highly effective in patients with HER2 overexpressing metastatic breast cancer who had failed previous therapies.[138] Randomised clinical trials are in progress to establish the safety and efficacy of bevacizumab in combination with chemotherapy, endocrine therapy, and trastuzumab in all subtypes of breast cancer.

Primary systemic therapies

Primary systemic therapy, also known as neoadjuvant or preoperative therapy, was initially used for management of locally advanced breast cancers that could be rendered technically operable. Neoadjuvant approaches have increasingly been championed for treatment of operable tumours, with the expectation of improved outcomes and possible breast-conservation surgery.[139,140] Downstaging might reduce the requirement for mastectomy by up to half, and breast-conservation surgery is more likely for unifocal tumours located away from the nipple areolar complex.[141,142] Since the primary tumour remains in situ, primary systemic therapy allows serial core biopsies to be undertaken with monitoring of treatment effects. Primary systemic therapy constitutes a powerful in-vivo model providing potential information about pathological and molecular predictors of response and tumour biology, which in conjunction with imaging parameters, enables non-responders to be identified early and therapy changed accordingly.

Early trials of primary systemic therapy compared the same schedule of chemotherapy before or after standard surgical treatment. The NSABP B-18 trial randomised patients to four cycles of anthracycline-based chemotherapy before or after surgery. Overall survival was equivalent for both approaches, but patients receiving primary systemic therapy were more likely to undergo breast-conservation surgery.[141,142] However, rates of IBTR were higher when surgery followed rather than preceded chemotherapy, but this difference did not reach statistical significance (10·7% *vs* 7·6%, p=0·12).[142] Patients with a complete pathological response to primary systemic therapy have improved disease-free and overall survival, suggesting its use as a surrogate marker for trials comparing different schedules of primary systemic therapy.[141,143–145] The next generation of trials of primary systemic therapy aimed to establish whether different preoperative regimens could improve outcomes. In a small randomised trial, addition of docetaxel to a preoperative schedule compared with further anthracycline drugs doubled the complete pathological response with lengthening of disease-free and overall survival at 3 years.[146] By contrast, NSABP B-27 confirmed a doubling of the complete pathological response with addition of four cycles of docetaxel to four cycles of AC, but no improvement in overall survival.[147] Nonetheless, NSABP B-27 did show improved outcomes for patients who achieved a complete pathological response irrespective of schedule received.[147] Unlike adjuvant therapy trials, fewer numbers of patients and shorter follow-up are needed for assessment of primary systemic therapy. The activity of trastuzumab in the adjuvant setting has confirmed the benefits of this agent

when combined with chemotherapy in the neoadjuvant setting; complete pathological response rate more than doubled for combined therapy versus chemotherapy alone.[148] However, the potential for omission of surgical resection in patients with a complete pathological response remains limited in the absence of good clinico-radio-pathological correlation and prospective identification of this subset with imaging and percutaneous biopsy.

Oestrogen-receptor-negative tumours have higher rates of complete pathological response to primary chemotherapy than do hormone-sensitive tumours that exhibit lower rates.[147–150] Material from core biopsies or fine-needle aspirates can be processed for construction of DNA microarrays, allowing comparison of expression profiles between responders and non-responders.[151,152] A meta-analysis of neoadjuvant versus adjuvant systemic therapy for early-stage breast cancer shows that disease-free and overall survival are comparable for the two schedules.[153] Even if surgery causes a systemic perturbation that can be offset by induction chemotherapy, the assumption that a modest shift in the timing of chemotherapy relative to surgery would have any significant clinical effect is perhaps naive.[154] Moreover, increased rates of IBTR for neoadjuvant regimens could suggest inadequate surgery and cast doubt on the model of downstaging to allow breast-conservation surgery.

By analogy with neoadjuvant chemotherapy, hormonal treatment can be used preoperatively to downstage tumours. Hormonal therapies are less toxic and potential side-effects of chemotherapy can be avoided in elderly receptor-positive-patients and those with a poor performance status.[155] Moreover, oestrogen-receptor-positive patients are less likely to achieve a complete pathological response with primary chemotherapy than oestrogen-receptor-negative patients are.[147,149,150] Most studies relate to postmenopausal women for whom the aromatase inhibitors have consistently outperformed tamoxifen in the neoadjuvant setting, when endpoints include response rates and breast-conservation rates.[156,157] The amount of oestrogen-receptor expression is the main determinant of response, and the optimum duration of therapy might be longer than for chemotherapy.[158] In a study of patients with hormonally-sensitive locally-advanced and inoperable breast cancer, letrozole given as a preoperative schedule for 4 months yielded significantly better response rates than did tamoxifen for a similar period and allowed a significantly higher rate of breast-conservation surgery.[156] The IMPACT study randomised patients with operable hormone-responsive breast cancer to 3 months of anastrozole alone, tamoxifen alone, or a combination of the two. No significant difference in objective clinical response rates were recorded, but anastrozole was more effective than tamoxifen was in reducing Ki-67 expression and downstaging tumours to allow breast-conservation surgery according to surgeon assessment.[157]

Tumours do not necessarily shrink in a concentric manner in response to chemotherapy. Even if no viable cancer cells remain at the site of the original tumour periphery, this zone might contain unstable epithelium that is prone to malignant change.[159] Furthermore, tumour regression is difficult to assess radiologically even with MRI.[160] Functional imaging techniques have a potential role in assessment of disease extent before and after chemotherapy and can be especially useful in early assessment of tumour response as changes in metabolism, cell proliferation, and vascularity precede tumour regression.[161]

Primary systemic therapy can cause differential downstaging between sentinel and non-sentinel lymph nodes.[162] Biopsy of sentinel lymph nodes undertaken before chemotherapy will keep the risk of a false-negative result to a minimum and ensure that decisions for postmastectomy radiotherapy are based on accurate nodal staging.[163] However, there is no quantification of regional metastatic load, and some advocate biopsy of sentinel lymph nodes after primary systemic therapy to take advantage of nodal downstaging and avoidance of axillary dissection in up to 40% of patients.[162]

Chemoprevention

Tamoxifen is a pioneering non-steroidal antioestrogen whose primary action is to competitively antagonise oestrogen at the cellular-receptor level.[164] It has a proven efficacy in treatment of breast cancer over the past 30 years,[165] with substantial increases in survival in patients receiving long-term adjuvant therapy.[166] Furthermore, patients receiving adjuvant tamoxifen have a 47% reduction of contralateral tumours.[167] This accrual of a vast clinical database, underpinned by data from preclinical models and in-vitro studies,[168] catalysed the exploration of tamoxifen as a chemopreventive in high-risk women.[169] Several placebo-controlled chemoprevention trials of tamoxifen in high-risk premenopausal and postmenopausal women have shown up to a 50% reduction in the cumulative incidence of both invasive and non-invasive breast cancer, with primary effects confined to oestrogen-receptor-positive disease.[170,171] Moreover, recent data suggest that not only is tamoxifen effective during therapy, but also that chemoprevention is enhanced for many years after treatment ends.[171–173] This important observation shows the continuing antitumour action of tamoxifen, which occurs at a time when there are very few side-effects from the drug. The side-effect profile of tamoxifen and other potential agents are crucial considerations in the chemopreventive setting when the risk to benefit ratio is shifted and healthy women receive a pharmacological intervention for which the benefits are less tangible.

A modest increase in endometrial cancer in postmenopausal women has been well documented,[171] although neither this increase nor a raised risk of thromboembolism has been noted in premenopausal women.[171] Tamoxifen can result in hot flushes when used as adjuvant therapy in patients with breast cancer and is

a potential cause of non-compliance. This side-effect is especially pertinent in women who are considering use of tamoxifen for chemoprevention, and a selective serotonin reuptake inhibitor often needs to be co-prescribed. However, the latter can interfere with conversion of tamoxifen to its active metabolite endoxifen and should not be used;[174] the occurrence of hot flushes can indicate effective metabolism.[175] Additionally, mutations in *CYP2D6* can impede conversion of tamoxifen to endoxifen and might be relevant to patients considering use of tamoxifen for chemoprevention.

Concerns over increased incidence of endometrial cancer in women taking tamoxifen have led to re-assessment of other non-steroidal antioestrogens with attenuated uterotrophic activity in the rodent uterus.[176] The recognition that non-steroidal antioestrogens such as tamoxifen and raloxifene were selective oestrogen-receptor modulators with duality of action created a new dimension in therapeutics that is being exploited in chemoprevention strategies. If a selective oestrogen-receptor modulator is oestrogenic in bone but antioestrogenic in breast tissue, then perhaps it could be used to prevent osteoporosis with concomitant prophylaxis of breast cancer in postmenopausal women.[177] Raloxifene has been successfully tested for reduction of fractures in women at high risk for osteoporosis[178] and significantly reduces the incidence of oestrogen-receptor-positive breast cancer (77% risk reduction) in patients receiving long-term raloxifene for prevention of this disease.[179] These encouraging findings combined with the desire to minimise side-effects sporned the STAR trial:[180] a head-to-head comparison of tamoxifen and raloxifene as chemopreventive agents in high-risk postmenopausal women. Initial results have shown that raloxifene is equivalent to tamoxifen in reducing the incidence of oestrogen-receptor-positive breast cancer by 50%, but is less effective in prevention of non-invasive disease.[180] Raloxifene might therefore interfere with the progression of in-situ to invasive disease, but have no effect on premalignant to in-situ transition. Raloxifene had a more favourable side-effect profile than did tamoxifen, with marginally significant reductions of thromboembolic events, cataracts, lens replacement, and endometrial cancer.

The panel summarises US recommendations for use of selective oestrogen-receptor modulators on the basis of clinical-trial evidence and approvals from the Food and Drug Administration for risk reduction.[171,181] Recommendations for treatment duration are a single pulse of 5 years. However, the long-term use of raloxifene to prevent osteoporosis could mandate 10 or more years of therapy, but the apparent carry-over effect maintains the antitumour efficacy of raloxifene and tamoxifen beyond the actual treatment period.[180]

Future research should be directed at elucidating the mechanism of action of selective oestrogen-receptor modulators in different target tissues around the body. The configuration of the ligand/oestrogen receptor complex determines the recruitment of co-activators and co-repressors that bind to the external surface of the complex and activate oestrogen-response elements.[182] Individual selective oestrogen-receptor modulators have a clinical signature, with a range of structure-activity profiles that are site specific and confer differential and non-correlative mixed agonist or antagonist activity between species and tissues. Finally, clinical trials are assessing aromatase inhibitors in high-risk postmenopausal women as chemopreventive agents. IBIS II is a multicentre trial[183] that randomises healthy women at increased risk of breast cancer to either anastrozole or placebo. These inhibitors are associated with a greater reduction of contralateral breast cancer in adjuvant trials than is tamoxifen. They could potentially be combined with an luteinising hormone-releasing hormone agonist as a chemopreventive strategy in premenopausal women, but concerns exist about side-effects of profound oestrogen deprivation, and the optimum duration of therapy is unknown.

***Panel:* US recommendations for use of selective oestrogen-receptor modulators**

Tamoxifen

Recommended for high-risk premenopausal women for whom there is no significantly increased risk of endometrial cancer or blood clots

Raloxifene

Recommended for high-risk postmenopausal women for whom there is no significantly increased risk of endometrial cancer

Raloxifene

Recommended for treatment and prevention of osteoporosis. It reduces the risk of breast cancer with no increased risk of endometrial cancer

Conclusions

Despite an inexorable rise in the incidence of breast cancer, improvements in treatments together with screening have led to modest falls in mortality. Local control of disease does affect overall survival, and greater attention to surgical margins and improved radiotherapy techniques have reduced local recurrence after breast-conservation surgery. Oncoplastic surgical techniques are being used selectively to enhance cosmetic outcomes while satisfying oncological mandates. Long-term outcome is determined by the presence and behaviour of distant micrometastases, which have to be effectively managed to achieve disease control if not cure. Molecular profiling offers the potential to provide predictive information about individual tumour response, which will guide clinical application of targeted biological therapies and rationalise their integration with conventional systemic treatments.

Conflicts of interest

We declare that we have no conflicts of interest.

References

1 Hortobagyi GN, de la Garza Salazar J, Pritchard K, et al. The global breast cancer burden: variations in epidemiology and survival. *Clin Breast Cancer* 2005; **6:** 391–401.

2 Porter P. "Westernizing" women's risks? Breast cancer in lower-income countries. *N Engl J Med* 2008; **358:** 213–16.

3 Hankinson SE, Colditz GA, Willett WC. Towards an integrated model for breast cancer etiology: the lifelong interplay of genes, lifestyle, and hormones. *Breast Cancer Res Treat* 2004; **6:** 213–18.

4 Ravdin PM, Cronin KA, Howlader N, et al. The decrease in breast-cancer incidence in 2003 in the United States. *N Engl J Med* 2007; **356:** 1670–74.

5 Beral V, Hermon C, Reeves G, Peto R. Sudden fall in breast cancer death rates in England and Wales. *Lancet* 1995; **345:** 1642–43.

6 Peto R, Boreham J, Clarke M, Davies C, Beral V. UK and USA breast cancer deaths down 25% in year 2000 at ages 20–69 years. *Lancet* 2000; **355:** 1822.

7 Jatoi I, Miller AB. Why is breast-cancer mortality declining? *Lancet Oncol* 2003; **4:** 251–54.

8 Berry DA, Cronin KA, Plevritis SK, et al. Effect of screening and adjuvant therapy on mortality from breast cancer. *N Engl J Med* 2005; **353:** 1784–92.

9 Jatoi I, Chen BE, Anderson WF, Rosenberg PS. Breast cancer mortality trends in the United States according to estrogen receptor status and age at diagnosis. *J Clin Oncol* 2007; **25:** 1683–90.

10 Anderson WF, Jatoi I, Devesa SS. Distinct breast cancer incidence and prognostic patterns in the NCI's SEER program: suggesting a possible link between etiology and outcome. *Breast Cancer Res Treat* 2005; **90:** 127–37.

11 Clemmesen J. Carcinoma of the breast; results from statistical research. *Br J Rad* 1948; **21:** 583–90.

12 Adami HO, Hansen J, Jung B, Rimsten AJ. Age at first birth, parity and risk of breast cancer in a Swedish population. *Br J Cancer* 1980; **42:** 651–58.

13 Cleary MP, Maihle NJ. The role of body mass index in the relative risk of developing premenopausal versus postmenopausal breast cancer. *Proc Soc Exp Biol Med* (*New York*) 1997; **216:** 28–43.

14 Anderson WF, Matsuno RK, Sherman ME, et al. Estimating age-specific breast cancer risks: a descriptive tool to identify age interactions. *Cancer Causes Control* 2007; **18:** 439–47.

15 Byrne C, Schairer C, Wolfe J, et al. Mammographic features and breast cancer risk: effects with time, age and menopausal status. *J Natl Cancer Inst* 1995; **87:** 1622–29.

16 Jatoi I, Anderson WF, Rao SR, Devesa SS. Breast cancer trends among black and white women in the United States. *J Clin Oncol* 2005; **23:** 7836–41.

17 Jatoi I, Becher H, Leake CR. Widening disparity in survival between white and African-American patients with breast carcinoma treated in the US Department of Defense Healthcare system. *Cancer* 2003; **98:** 894–99.

18 Robson M, Offit K. Clinical practice. Management of an inherited predisposition to breast cancer. *N Engl J Med* 2007; **357:** 154–62.

19 Ford D, Easton DF. The genetics of breast and ovarian cancer. *Br J Cancer* 1995; **72:** 805–12.

20 Merajver SD, Pham TM, Caduff RF, et al. Somatic mutations in the BRCA1 gene in sporadic ovarian tumours. *Nat Genet* 1995; **9:** 439–43.

21 Baynes C, Healey CS, Pooley KA, et al. Common variants in the ATM, BRCA-1, BRCA-2, CHEK2 and TP53 cancer susceptibility genes are unlikely to increased breast cancer risk. *Breast Cancer Res Treat* 2007; **9:** R27.

22 Ramazzini B. De Morbis Artificum. Editio Secunda. Ultrajecti: Apud Guilielmum van de Water Academiae Typographum (courtesy, The Bodleian Library, Oxford): 156.

23 Petrek JA, Dukoff R, Rogatko A. Prognosis of pregnancy-associated breast cancer. *Cancer* 1991; **67:** 869–72.

24 Colditz GA. Estrogen, estrogen plus progestin therapy, and risk of breast cancer. *Clin Cancer Res* 2005; **11:** 909–17.

25 Holmberg L, Iversen O-E, Rudenstam CM, et al. Increased risk of recurrence after hormone replacement therapy in breast cancer survivors. *J Natl Cancer Inst* 2008; **100:** 475–82.

26 Monninkhof EM, Elias SG, Vlems FA, et al. Physical activity and breast cancer: a systematic review. *Epidemiology* 2007; **18:** 137–57.

27 Zhang SM, Lee IM, Manson JE, Cook NR, Willett WC, Buring JE. Alcohol consumption and breast cancer risk in the Women's Health Study. *Am J Epidemiol* 2007; **165:** 667–76.

28 Santen RJ, Boyd NF, Chlebowski RT, et al. Critical assessment of new risk factors for breast cancer: considerations for development of an improved risk prediction model. *Endocr Relat Cancer* 2007; **14:** 169–87.

29 Smith LF. Palpable cancer of the breast and negative mammography: the ongoing dilemma. *J Surg Oncol* 2007; **96:** 451–52.

30 Zonderland HM, Coerkamp EG, Hermans J, et al. Diagnosis of breast cancer: contributions of US as an adjunct to mammography. *Radiology* 1999; **213:** 413–22.

31 Britton PD, McCann J. Needle biopsy in the NHS Breast Screening Programme: how much and how accurate? *Breast* 1999; **8:** 5–11.

32 Stanley MW, Sidawy MK, Sanchez MA, Stahl RE, Goldfischer M. Current issues in breast cytopathology. *Am J Clin Path* 2000; **115:** S49–75.

33 Helbich TH, Matzek W, Fuchsjager MH. Stereotactic and ultrasound-guided breast biopsy. *Eur Radiol* 2004; **14:** 383–93.

34 Jackman RJ, Nowels KW, Rodriguez-Soto J, et al. Sterotactic, automated, large-core needle biopsy of nonpalpable breast lesions: false-negative and histologic underestimation rates after long term follow up. *Radiology* 1999; **210:** 799–805.

35 DeMartini W, Lehman C, Partridge S. Breast MRI for cancer detection and characterization: a review of evidence-based clinical applications. *Acad Radiol* 2008; **15:** 408–16.

36 Mameri CS, Kemp C, Goldman SM, et al. Impact of breast MRI on surgical treatment, axillary approach, and systemic therapy for breast cancer. *Breast J* 2008; **14:** 236–44.

37 Morrow M, Freedman G. A clinical oncology perspective on the use of breast MR. *Magn Reson Imaging Clin N Am* 2006; **14:** 363–78.

38 Solin LJ, Orel SG, Hwang WT, et al. Relationship of breast magnetic resonance imaging to outcome after breast conservation treatment with radiation for women with early stage invasive breast carcinoma or ductal carcinoma in situ. *J Clin Oncol* 2008; **26:** 386–91.

39 Morrow M. Magnetic resonance imaging in the breast cancer patient: curb your enthusiasm. *J Clin Oncol* 2008; **26:** 352–53.

40 Gotzsche PC, Nielsen M. Screening for breast cancer with mammography. *Cochrane Database Syst Rev* 2006; **3:** CD001877.

41 Moss SM, Cuckle H, Evans A, Johns L, Waller M, Bobrow L. Effect of mammographic screening from age 40 years on breast cancer mortality at 10 years' follow-up: a randomised controlled trial. *Lancet* 2006; **368:** 2053–60.

42 Barton MB, Harris R, Fletcher SW. The rational clinical examination. Does this patient have breast cancer? The screening clinical breast examination: should it be done? How? *JAMA* 1999; **282:** 1270–80.

43 Thomas DB, Gao DL, Ray RM, et al. Randomized trial of breast self-examination in Shanghai: final results. *J Natl Cancer Inst* 2002; **94:** 1445–57.

44 Saslow D, Boetes C, Burke W, et al. American Cancer Society guidelines for breast screening with MRI as an adjunct to mammography. *CA Cancer J Clin* 2007; **57:** 75–89.

45 Querci della Rovere G, Benson JR. Ipsilateral local recurrence of breast cancer: determinant or indicator of poor prognosis? *Lancet Oncol* 2002; **3:** 183–87.

46 Fisher B, Anderson S, Bryant J, et al. Twenty-year follow up of a randomized trial comparing total mastectomy, lumpectomy and lumpectomy plus irradiation for the treatment of invasive breast cancer. *N Engl J Med* 2002; **347:** 1233–41.

47 Fisher B. Laboratory and clinical research in breast cancer—a personal adventure. The David A Karnofsky Memorial Lecture. *Cancer Res* 1980; **40:** 3863–74.

48 Komoike Y, Akiyama F, Lino Y, et al. Ipsilateral breast tumour recurrence (IBTR) after breast conserving treatment for breast cancer. *Cancer* 2005; **106:** 35–39.

49 Early Breast Cancer Trialists Collaborative Group. Effects of radiotherapy and of differences in the extent of surgery for early breast cancer on local recurrence and 15 year survival: an overview of the randomised trials. *Lancet* 2005; **366:** 2087–106.

50 Huang E, Cheng SH, Dressman H, et al. Gene expression predictors of breast cancer outcomes. *Lancet* 2003; **361:** 1590–96.

51 Locker G, Sainsbury R, Cuzick J. Breast surgery in the ATAC trial: women in the United States are more likely to have mastectomy. *Breast Cancer Res Treat* 2002; **76:** S35.

52 IBTR. Breast cancer model. http://www.nemc.org/ibtr (accessed Nov 17, 2008).

53 Taghian A, Mohiuddin M, Jagsi R, et al. Current perceptions regarding surgical margin status after breast conserving therapy: results of a survey. *Ann Surg* 2005; **241:** 629–39.

54 Singletary SE. Surgical margins in patients with early stage breast cancer treated with breast conservation therapy. *Am J Surg* 2002; **184:** 383–93.

55 Morrow M, Harris JR. Practice guidelines for breast conserving therapy in the management of invasive breast cancer. *J Am Coll Surg* 2007; **205:** 362–76.

56 Cochrane R, Valasiadou P, Wilson A, et al. Cosmesis and satisfaction after breast conserving surgery correlates with percentage of breast volume excised. *Br J Surg* 2003; **90:** 1505–09.

57 Taylor ME, Perez CA, Halverson KJ, et al. Factors influencing cosmetic results after conservation therapy for breast cancer. *In J Rad Oncol Biol Phys* 1995; **31:** 753–64.

58 McCulley SJ, Macmillan RD. Planning and use of therapeutic mammoplasty–Nottingham approach. *Br J Plast Surg* 2005; **58:** 889–901.

59 Asgeirsson K, McCulley S, Pinder S, Macmillan R. Size of invasive breast cancer and risk of local recurrence after breast conservation therapy. *Eur J Cancer* 2003; **39:** 2462–69.

60 Benson JR, Absar MS. Volume replacement and displacement techniques in oncoplastic surgery. Advances in Breast Cancer 2008; **5:** 1–7.

61 Rivadeniera DE, Simmons RM, Fish SK, et al. Skin-sparing mastectomy with immediate breast reconstruction: a critical analysis of local recurrence. *Cancer J* 2000; **6:** 331–35.

62 Overgaard M, Hansen PS, Overgaard J, et al. Post-operative radiotherapy in high risk pre-menopausal women with breast cancer who receive adjuvant chemotherapy. *N Engl J Med* 1997; **337:** 949–55.

63 Ragaz J, Jackson SM, Le N, et al. Adjuvant radiotherapy and chemotherapy in node positive pre-menopausal women with breast cancer. *N Engl J Med* 1997; **337:** 956–62.

64 Behranwala KA, Dua RS, Ross GM, et al. The influence of radiotherapy on capsule formation and aesthetic outcome after immediate breast reconstruction using biodimensional anatomical expander implants. *J Plast Reconstr Aesthet Surg* 2006; **59:** 1043–51.

65 Lyman GH, Guiliano AE, Somerfield MR, et al. The Americal Society of Clinical Oncology Guideline Recommendations for Sentinel Lymph Node Biopsy in Early Stage Breast Cancer. *J Clin Oncol* 2005; **23:** 7703–20.

66 Benson JR, Querci della Rovere G. Management of the axilla in women with breast cancer. *Lancet Oncol* 2007; **8:** 331–48.

67 Krag DN, Anderson SJ, Julian TB, et al. Technical outcomes of sentinel-lymph-node resection and conventional axillary-lymph-node dissection in patients with clinically node-negative breast cancer: results from the NSABP B-32 randomised phase III trial. *Lancet Oncol* 2007; **8:** 881–88.

68 Pal A, Provenzano E, Duffy SW, et al. A model for predicting non-sentinel lymph node metastatic disease when the sentinel lymph node is positive. *Br J Surg* 2008; **95:** 302–09.

69 Park J, Fey JV, Naik AM, et al. A declining rate of completion axillary dissection in sentinel lymph node positive breast cancer patients is associated with the use of a multivariate nomogram. *Breast Cancer Res Treat* 2005; **100:** S80 (abstract 2001).

70 Julian TB, Blumencranz P, Deck K, et al. Novel intraoperative molecular test for sentinel lymph node metastasesin patients with early stage breast cancer. *J Clin Oncol* 2008; **26:** 3338–45.

71 Naik AM, Fey J, Gemignani M, et al. The risk of axillary relapse after sentinel lymph node biopsy for breast cancer is comparable with that of axillary lymph node dissection. *Ann Surg* 2004; **240:** 462–71.

72 Kujit GP, Roumen RMH. Second thoughts on sentinel lymph node biopsy in node negative breast cancer. *Br J Surg* 2008; **95:** 310–11.

73 Veronesi U, Cascinelli N, Mariani L, et al. Twenty-year follow-up of a randomized study comparing breast-conserving surgery with radical mastectomy for early breast cancer. *N Engl J Med* 2002; **347:** 1227–32.

74 Smith IE, Ross GM. Breast radiotherapy after lumpectomy—no longer always necessary. *N Engl J Med* 2004; **351:** 1021–23.

75 Smith BD, Gross CP, Smith GL, et al. Effectiveness of radiation therapy for older women with early breast cancer. *J Natl Cancer Inst* 2006; **98:** 681–90.

76 Clark RM, McCulloch PB, Levine MN, et al. Randomized clinical trial to assess the effectiveness of breast irradiation following lumpectomy and axillary dissection for node-negative breast cancer. *J Natl Cancer Inst* 1992; **84:** 683–89.

77 Hughes KS, Schnaper LA, Berry D, et al. Lumpectomy plus tamoxifen with or without irradiation in women 70 years of age or older with early breast cancer. *N Engl J Med* 2004; **351:** 971–77.

78 Fyles AW, McCready DR, Manchul LA, et al. Tamoxifen with or without breast irradiation in women 50 years of age or older with early breast cancer. *N Engl J Med* 2004; **351:** 963–70.

79 King TA, Bolton JS, Kuske RR, et al. Long-term results of wide-field brachytherapy as the sole method of radiation therapy after segmental mastectomy for T(is,1,2) breast cancer. *Am J Surg* 2000; **180:** 299–304.

80 Cuttino LW, Arthur DW, Todor DA, et al. CT- guided multi-catheter insertion technique for partial breast brachytherapy (PBB): Reliable target coverage and dose homogeneity. *Brachytherapy* 2003; **2:** 41–68.

81 Vicini FA, Kestin L, Chen P, et al. Limited-field radiation therapy in the management of early-stage breast cancer. *J Natl Cancer Inst* 2003; **95:** 1205–10.

82 Kuske RR, Winter K, Arthur DW, et al. Phase II trial of brachytherapy alone after lumpectomy for select breast cancer: toxicity analysis of RTOG 95-17. *Int J Radiat Oncol Biol Phys* 2006; **65:** 45–51.

83 Vaidya JS, Baum M, Tobias JS, et al. Targeted intra-operative radiotherapy (Targit): an innovative method of treatment for early breast cancer. *Ann Oncol* 2001; **12:** 1075–80.

84 Veronesi U, Orrechia R, Luini A, et al. A preliminary report of intraoperative radiotherapy (IORT) in limited-stage breast cancers that are conservatively treated. *Eur J Cancer* 2001; **37:** 2178–83.

85 Enderling H, Chaplain MA, Anderson AR, Vaidya JS. A mathematical model of breast cancer development, local treatment and recurrence. *J Theor Biol* 2007; **246:** 245–59.

86 Belletti B, Vaidya JS, D'Andrea S, et al. Targeted intraoperative radiotherapy impairs the stimulation of breast cancer cell proliferation and invasion caused by surgical wound healing. *Clin Cancer Res* 2008; **14:** 1325–32.

87 Keisch M, Vicini F, Kuske RR, et al. Initial clinical experience with the MammoSite breast brachytherapy applicator in women with early-stage breast cancer treated with breast-conserving therapy. *Int J Radiat Oncol Biol Phys* 2003; **55:** 289–93.

88 Benitez PR, Keisch ME, Vicini F, et al. Five-year results: the initial clinical trial of MammoSite balloon brachytherapy for partial breast irradiation in early-stage breast cancer. *Am J Surg* 2007; **194:** 456–62.

89 Vicini F, Beitch PD, Quiet CA, et al. Three-year analysis of treatment efficacy, cosmesis, and toxicity by the American Society of Breast Surgeons MammoSite Breast Brachytherapy Registry Trial in patients treated with accelerated partial breast irradiation (ABPI). *Cancer* 2008; **112:** 758–66.

90 Vicini FA, Remouchamps V, Wallace M, et al. Ongoing clinical experience utilizing 3D conformal external beam radiotherapy to deliver partial-breast irradiation in patients with early-stage breast cancer treated with breast-conserving therapy. *Int J Radiat Oncol Biol Phys* 2003; **57:** 1247–53.

91 Formenti SC, Truong MT, Goldberg JD, et al. Prone accelerated partial breast irradiation after breast-conserving surgery: preliminary clinical results and dose-volume histogram analysis. *Int J Radiat Oncol Biol Phys* 2004; **60:** 493–504.

92 Kestin LL, Sharpe MB, Frazier RC, et al. Intensity modulation to improve dose uniformity with tangential breast radiotherapy: initial clinical experience. *Int J Radiat Oncol Biol Phys* 2000; **48:** 1559–68.

93 Whelan T, MacKenzie R, Julian J, et al. Randomized trial of breast irradiation schedules after lumpectomy for women with lymph node-negative breast cancer. *J Natl Cancer Inst* 2002; **94:** 1143–50.

94 The START trialists' Group. The UK Standardisation of Breast Radiotherapy (START) Trail A of radiotherapy hypofractionation for treatment of early breast cancer: a randomised trial. *Lancet Oncol* 2008; **9:** 331–41.

95 Kruegrer EA, Fraass BA, McShan DL, et al. Potential gains for irradiation of chest wall and regional nodes with intensity modulated radiotherapy. *Int J Radiat Oncol Biol Phys* 2003; **56:** 1023–37.

96 MRC SUPREMO Trial. http://www.supremo-trial.com (accessed Nov 17, 2008).

97 Early Breast Cancer Trialists' Collaborative Group. Polychemotherapy for early breast cancer: an overview of the randomised trials. *Lancet* 1998; **352:** 930–42.

98 Early Breast Cancer Trialists Collaborative Group. Tamoxifen for early breast cancer: an overview of the randomised trials. *Lancet* 1998; **351:** 1451–61.

99 Ravdin PM, Siminoff LA, Davis GJ, et al. Computer program to assist in making decisions about adjuvant therapy for women with early breast cancer. *J Clin Oncol* 2001; **19:** 980–91.

100 Marchionni L, Wilson RF, Wolff AC, et al. Systematic review: gene expression profiling assays in early stage breast cancer. *Ann Intern Med* 2008; **148:** 358–69.

101 Harris L, Fritsche H, Mennel R, et al. American Society of Clinical Oncology 2007 update of recommendations for the use of tumor markers in breast cancer. *J Clin Oncol* 2007; **25:** 5287–12.

102 Scottish Cancer Trials Breast Group and IBU. Adjuvant ovarian ablation versus CMF chemotherapy in premenopausal women with pathological stage II breast carcinoma: the Scottish trial. *Lancet* 1993; **341:** 1293–98.

103 Lyman GH, Guiliano AE, Somerfield MR, et al. The American Society of Clinical Oncology Guideline Recommendations for Sentinel Lymph Node Biopsy in Early Stage Breast Cancer. *J Clin Oncol* 2005; **23:** 7703–20.

104 ATAC Trialist's Group. Results of the ATAC (Arimidex, Tamoxifen, Alone or in Combination) trial after completion of 5 years adjuvant treatment for breast cancer. *Lancet* 2005; **365:** 60–62.

105 The Arimidex, Tamoxifen, Alone or in Combination (ATAC) Trialists' Group. Effect of anastrozole and tamoxifen as adjuvant treatment for early stage breast cancer: 100 month analysis of the ATAC trial. *Lancet Oncol* 2008; **9:** 45–53.

106 Benson JR. The use or aromatase inhibitors in post-menopausal women with hormone receptor positive breast cancer. *J Clin Oncol* 2005; **23:** 6807–09.

107 Coombes RC, Kilburn LS, Snowdon CF, et al. Survival and safety of exemestane versus tamoxifen after 2–3 year's tamoxifen treatment (Intergroup Exemestane Study): a randomised controlled trial. *Lancet* 2007; **369:** 559–70.

108 Jonat W, Gnant M, Boccado F, et al. Effectiveness of switching from adjuvant tamoxifen to anastrozole in postmenopausal women with hormone-sensitive early-stage breast cancer: a meta-analysis. *Lancet Oncol* 2006; **7:** 991–96.

109 Coates AS, Keshaviah A, Thurlimann B, et al. Five years of letrozole compared with tamoxifen as initial therapy for postmenopausal women with endocrine responsive early breast cancer: update of study BIG 1-98. *J Clin Oncol* 2007; **25:** 486–92.

110 Mouridsen H, Giobbie-Hurder A, Mauriac L, et al. BIG 1-98: a randomized double-blind phase III study evaluating letrozole and tamoxifen in sequence as adjuvant endocrine therapy for postmenopausal women with receptor-positive breast cancer. 31st San Antonio Breast Cancer Symposium, Texas, USA; December, 2008.

111 Goss PE, Ingle JN, Martino S, et al. Randomised trial of letrozole following tamoxifen as extended adjuvant therapy in receptor-positive breast cancer: updated findings from NCIC CTG MA.17. *J Natl Cancer Inst* 2005; **97:** 1262–71.

112 Clarke M, Coates AS, Darby SC, et al. Adjuvant chemotherapy in oestrogen receptor poor breast cancer: patient level meta-analysis of randomised trials. *Lancet* 2008; **371:** 29–40.

113 Carlson RW, Brown E, Burstein HJ, et al. NCCN Task Force Report: adjuvant therapy for breast cancer. *J Natl Compr Cancer Netw* 2006; **4** (suppl)**:** S1–26.

114 Paik S, Shak S, Tang G, et al. A multigene assay to predict recurrence of tamoxifen-treated, node negative, estrogen receptor positive breast cancer. *J Clin Oncol* 2006; **24:** 3726–34.

115 Roche H, Fumoleau P, Spielman M, et al. Sequential adjuvant epirubicin based and docetaxel chemotherapy for node positive breast cancer patients: The FNCLCC PACS001 trial. *J Clin Oncol* 2006; **24:** 5664–71.

116 Albain KS, Barlow W, Shak S, et al. Prognostic and predictive value of the 21-gene recurrence score assay in postmenopausal, node positive, ER positive breast cancer. *Breast Cancer Res Treat* 2007; **96:** 10A.

117 Esteva FJ, Sahin AA, Cristofanilli M, et al. Prognostic role of a multigene reverse transcriptase-PCR assay in patients with node-negative breast cancer not receiving adjuvant systemic therapy. *Clin Cancer Res* 2005; **11:** 3315–19.

118 Sparano JA. TAILORx: trial assigning individualized options for treatment (Rx). *Clin Breast Cancer* 2006; **7:** 347–50.

119 Henderson IC, Berry DA, Demetri GD, et al. Improved outcomes from adding sequential Paclitaxel but not escalating Doxorubicin dose in an adjuvant chemotherapy regimen for patients with node positive primary breast cancer. *J Clin Oncol* 2003; **21:** 976–83.

120 Citron ML, Berry DA, Cirrincione C, et al. Randomised trial of dose-dense versus conventionally scheduled and sequential versus concurrent combination chemotherapy as postoperative adjuvant treatment of node positive primary breast cancer: first report of Intergroup Trial C. *J Clin Oncol* 2003; **21:** 1431–39.

121 Martin M, Pienkowski T, Mackay J, et al. Adjuvant docetaxol for node positive breast cancer. *N Engl J Med* 2005; **352:** 2302–13.

122 Sparano JA, Wang M, Martino S, et al. Weekly paclitaxel in the adjuvant treatment of breast cancer. *N Engl J Med* 2008; **358:** 1663–71.

123 Hess KR, Anderson K, Symmans WF, et al. Pharmacogenomic predictor of sensitivity to preoperative chemotherapy with Paclitaxel and Fluorouracil, Doxorubicin and Cyclophosphamide in breast cancer. *J Clin Oncol* 2006; **24:** 4236–44.

124 Ellis PA, Barrett-Lee PJ, Bloomfield D, et al. Preliminary results of the UK Taxotere as Adjuvant Chemotherapy (TACT) trial. *Breast Cancer Res Treat* 2007; **106:** S21 (abstract 78).

125 Hayes DF, Thor AD, Dressler LG, et al. HER2 and response to paclitaxel in node positive breast cancer. *N Engl J Med* 2008; **21:** 976–83.

126 Pritchard KI, Messersmith H, Elavathil L, et al. HER2 and topoisomerase II as predictors of response to chemotherapy. *J Clin Oncol* 2008; **26:** 736–44.

127 Slamon DJ, Clark GM, Wong SG, et al. Human breast cancer: correlation of relapse and survival with amplication of the HER2/neu oncogene. *Science* 1987; **235:** 177–82.

128 Wolff AC, Hammond ME, Schartz JN, et al. American Society of Clinical Oncology/College of American Pathologists guideline recommendations for human epidermal growth factor receptor 2 testing in breast cancer. *J Clin Oncol* 2007; **25:** 118–45.

129 Romond EH, Perez EA, Bryant J, et al. Trastuzumab plus adjuvant chemotherapy for operable HER2 positive breast cancer. *N Engl J Med* 2005; **353:** 1673–84.

130 Smith I, Procter M, Gelber RD, et al. 2-year follow-up of trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer: a randomised controlled trial. *Lancet* 2007; **369:** 29–36.

131 Perez EA, Suman VJ, Davidson NE, et al. Cardiac safety analysis of doxorubicin and cyclophosphamide followed by paclitaxel with or without trastuzumab in the North Central Cancer Treatment Group N9831 adjuvant breast cancer trial. *J Clin Oncol* 2008; **26:** 1231–38.

132 Cancer International Research Group.Press Release BCIRG 006 FDA Approval. May 29, 2008. http://64.233.183.104/search?q=cache:L6vhvabBD1QJ:www.bcirg.org/NR/rdonl (accessed Aug 7, 2008).

133 Wood ER, Truesdale AT, McDonald OB, et al. A unique structure for epidermal growth factor receptor bound to GW572016 (Lapatinib): relationships among protein conformation, inhibitor off-rate and receptor activity in tumour cells. *Cancer Res* 2004; **64:** 6652–59.

134 Geyer CE, Forster J, Lindquist D, et al. Lapatinib plus capecitibine for HER2 positive advanced breast cancer. *N Engl J Med* 2006; **355:** 2733–43.

135 Nahta R, Hung MC, Esteva FJ. The HER2 targetting antibodies trastuzumab and pertuzumab synergistically inhibit the survival of breast cancer cells. *Cancer Res* 2004; **64:** 2343–46.

136 Nahta R, Yuan LX, Zhang B, et al. Insulin-like growth factor I receptor/human epidermal growth factor receptor 2 heterodimerization contributes to trastuzumab resistance of breast cancer cells. *Cancer Res* 2005; **65:** 1118–28.

137 O'Reilly KE, Rojo F, She QB, et al. mTOR inhibition induces upstream receptor tyrosine kinase signaling and activates Akt. *Cancer Res* 2006; **66:** 1500–08.

138 Pegram M, Chan D, Cichmann RA, et al. Phase II combined biological therapy targeting the HER2 proto-oncogene and the vascular endothelial growth factor (VEGF) using trastuzumab and bevacizumab as first-line treatment of HER2 amplified breast cancer. *Breast Cancer Res Treat* 2006; **100:** abstract 201.

139 Hortobagyii GN, Ames FC, Buzdar AU, et al. Management of stage III primary breast cancer with primary chemotherapy, surgery and radiation therapy. *Cancer* 1988; **62:** 2507–16.

140 Wolff AC, Davidson NE. Primary systemic therapy in operable breast cancer. *J Clin Oncol* 2000; **18:** 1558–69.

141 Fisher B, Brown A, Mamounas E, et al. Effect of preoperative chemotherapy on local-regional disease in women with operable breast cancer: findings from National Surgical Adjuvant Breast and Bowel Project B-18. *J Clin Oncol* 1997; **15:** 2483–93.

142 Wolmark N, Wang J, Mamounas E, et al. Preoperative chemotherapy in patients with operable breast cancer: nine-year results from National Surgical Adjuvant Breast and Bowel Project B-18. *J Natl Cancer Inst Monogr* 2001; **30:** 96–102.

143 Van der Hage JA, van de Velde CJH, Julien J-P, et al. Preoperative chemotherapy in primary operable breast cancer: results from the European Organization for Research and Treatment of Cancer trial 10902. *J Clin Oncol* 2001; **19:** 4224–37.

144 Makris A, Powles TJ, Ashley SE et al. A reduction in the requirements for mastectomy in a randomized trial of neoadjuvant chemoendocrine therapy in primary breast cancer. *Ann Oncol* 1998; **9:** 1179–84.

145 Scholl SM, Fourquet A, Asselain B et al. Neoadjuvant vs adjuvant chemotherapy in premenopausal women with tumors considered too large for breast conserving surgery: preliminary results of a randomised trial. *Eur J Cancer* 1994; **30A:** 645–52.

146 Smith IC, Heys SD, Hutcheon AW, et al. Neoadjuvant chemotherapy in breast cancer: significantly enhanced response with docetaxel. *J Clin Oncol* 2002; **20:** 1456–66.

147 Bear HD, Anderson S, Brown A, et al. The effect of tumor response of adding sequential preoperative docetaxel to preoperative doxorubicin and cyclophosphamide: Preliminary results from National Surgical Adjuvant Breast and Bowel Project Protocol B-27. *J Clin Oncol* 2003; **21:** 4165–74.

148 Buzdar AU, Ibrahim NK, Francis D, et al. Significant higher pathologic complete remission rate after neoadjuvant therapy with trastuzumab, paclitaxel, and epirubicin chemotherapy: results of a randomised trial in human epidermal growth factor receptor 2-positive operable breast cancer. *J Clin Oncol* 2005; **23:** 3676–85.

149 Guarneri V, Broglio K, Kau SW, et al. Prognostic value of pathologic complete response after primary chemotherapy in relation to hormone receptor status and other factors. *J Clin Oncol* 2006; **24:** 1037–44.

150 Gianni L, Baselga J, Eirmann W, et al. Feasibility and tolerability of sequential doxorubicin/paclitaxel followed by cyclophosphamide, methotrexate, and fluorouracil and its effects on tumor response as preoperative therapy. *Clin Cancer Res* 2005; **11:** 8715–21.

151 Chang JC, Wooten EC, Tsimelzon A, et al. Gene expression profiling for the prediction of therapeutic response to docetaxel in patients with breast cancer. *Lancet* 2003; **362:** 362–69.

152 Ayers M, Symmans WF, Stec J, et al. Gene expression profiles predict complete pathological response to neoadjuvant paclitaxel and fluorouracil, doxorubicin, and cyclophosphamide chemotherapy in breast cancer. *J Clin Oncol* 2004; **22:** 2284–93.

153 Mauri D, Pavlidis N, Ioannidis JP. Neoadjuvant versus adjuvant systemic treatment for breast cancer: a meta-analysis. *J Natl Cancer Inst* 2005; **97:** 188–194.

154 Davidson NE, Morrow M. Sometimes a great notion—an assessment of neoadjuvant systemic therapy for breast cancer. *J Natl Cancer Inst* 2005; **97:** 159–61.

155 Beresford MJ, Ravichandran D, Makris A. Neoadjuvant endocrine therapy in breast cancer. *Cancer Treat Rev* 2007; **33:** 48–57.

156 Eiermann W, Paepke S, Appfelastaedt J, et al. Pre-operative treatment of post-menopausal breast cancer with letrozole: a randomized double-blind multicenter study. *Ann Oncol* 2001; **12:** 1527–32.

157 Smith I, Dowsett M, Ebbs SR, et al. Neoadjuvant treatment of post-menopausal breast cancer with anastrozole, tamoxifen or both in combination: the Immediate Preoperative Anastrozole, Tamoxifen or Combined with Tamoxifen (IMPACT) Multicenter Double-Blind Randomized trial. *J Clin Oncol* 2005; **23:** 5108–16.

158 Dixon JM, Jackson J, Renshaw L, et al. Neoadjuvant tamoxifen and aromatase inhibitors: comparisons and clinical outcomes. *J Steroid Biochem Mol Biol* 2003; **86:** 295–99.

159 Veronesi U, Bonadonna G, Zurrida S, et al. Conservation surgery after primary chemotherapy in large carcinomas of the breast. *Ann Surg* 1995; **222:** 612–18.

160 Beresford M, Padhani AR, Goh V, et al. Imaging breast cancer response during neoadjuvant systemic therapy. *Expert Rev Anticancer Ther* 2005; **5:** 907–15.

161 Padhani AR, Ah-See M-L, Makris A. MRI in the detection and management of breast cancer. *Expert Rev Anticancer Ther* 2005; **5:** 239–52.

162 Mamounas EP, Brown A, Anderson S, et al. Sentinel node biopsy after neoadjuvant chemotherapy in breast cancer: results from National Surgical Adjuvant Breast and Bowel Project Protocol B-27. *J Clin Oncol* 2005; **23:** 2694–02.

163 Sabel MS, Schott AF, Kleer CG, et al. Sentinel node biopsy prior to neoadjuvant chemotherapy. *Am J Surg* 2003; **39:** 1089–96.

164 Jordan VC. Tamoxifen: a most unlikely pioneering medicine. *Nat Rev Drug Discov* 2003; **2:** 205–13.

165 Jensen EV, Jordan VC. The estrogen receptor: a model for molecular medicine. The Dorothy P Landon AACR Prize for Translational Research. *Clin Cancer Res* 2003; **9:** 1980–89.

166 Early Breast Cancer Trialists' Collaborative Group. Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomised trials. *Lancet* 2005; **365:** 1687–717.

167 Cuzick J, Baum M. Tamoxifen and contralateral breast cancer. *Lancet* 1985; **2:** 282.

168 Jordan VC. Tamoxifen: catalyst for the change to targeted therapy. *Eur J Cancer* 2008; **44:** 30–38.

169 Powles TJ, Hardy JR, Ashley SE, et al. A pilot trial to evaluate the acute toxicity and feasibility of tamoxifen for prevention of breast cancer. *Br J Cancer* 1989; **60:** 126–31.

170 Cuzick J, Powles T, Veronesi U, et al. Overview of the main outcomes in breast-cancer prevention trials. *Lancet* 2003; **361:** 296–300.

171 Fisher B, Costantino JP, Wickerham DL, et al. Tamoxifen for the prevention of breast cancer: current status of the National Surgical Adjuvant Breast and Bowel Project P-1 study. *J Natl Cancer Inst* 2005; **97:** 1652–62.

172 Cuzick J, Forbes JF, Sestak I, et al. Long term results of tamoxifen prophylaxis for breast cancer–96 month follow up of the randomized IBIS-I trial. *J Natl Camcer Inst* 2007; **99:** 272–82.

173 Powles TJ, Ashley S, Tidy A, et al. Twenty-year follow up of the Royal Marsden randomized, double blinded tamoxifen breast cancer prevention trial. *J Natl Cancer Inst* 2007; **99:** 283–90.

174 Stearns V, Johnson MD, Rae JM, et al. Active tamoxifen metabolite plasma concentrations after co-administration of tamoxifen and the selective serotonin reuptake inhibitor paroxetine. *J Natl Cancer Inst* 2003; **95:** 1758–64.

175 Goetz MP, Rae JM, Suman VJ, et al. Pharmacogenetics of tamoxifen biotransformation is associated with clinical outcomes of efficacy and hot flashes. *J Clin Oncol* 2005; **23:** 9312–18.

176 Black LJ, Jones CD, Falcone JF, et al. Antagonism of estrogen action with a new benzothiaphene derived antiestrogen. *Life Sci* 1983; **32:** 1031–36.

177 Jordan VC. Chemosuppression of breast cancer with tamoxifen: laboratory evidence and future clinical investigations. *Cancer Investl* 1988; **6:** 589–95.

178 Ettinger B, Black DM, Mitlak BH, et al. Reduction of vertebral fracture risk in postmenopausal women with osteoporosis treated with raloxifene: results from a 3-year randomized clinical trial Multiple Outcomes of Raloxifene Evaluation (MORE) Investigators. *JAMA* 1999; **282:** 637–45.

179 Martino S, Cauley JA, Barrett-Connor E, et al, for the CORE Investigators Continuing Outcomes Relevant to Evista. Breast cancer incidence in postmenopausal osteoporotic women in a randomised trial of raloxifene. *J Natl Cancer Inst* 2004; **96:** 1751–61.

180 Vogel VG, Costantino JP, Wickerham DL, et al. The Study of Tamoxifen and Raloxifene (STAR): Report of the National Surgical Adjuvant Breast and Bowel Project P-2 Trial. *JAMA* 2006; **295:** 2727–41.

181 Barrett-Connor E, Mosca L, Collins P, et al. Effects of raloxifene on cardiovascular events and breast cancer in postmenopausal women. *N Engl J Med* 2006; **355:** 125–37.

182 Jordan VC. Chemoprevention of breast cancer with selective oestrogen-receptor modulators. *Nature Rev* 2007; **7:** 46–53.

183 Cuzick J. Aromatase inhibitors in prevention–data from the ATAC trial and the design of IBIS-II (the second International Breast Cancer Intervention Study). *Recent Results Cancer Res* 2003; **163:** 96–103.