clinical skills to assess for potential risks of CAM use when evidence in the literature is lacking. ✣

Declaration of competing interests

The authors declare that they have no competing interests.

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Breast cancer diagnosis and treatment: an update

Epidemiology

Breast cancer is the most common cancer in the UK.[1] There are approximately 44,600 women and 300 men diagnosed each year in the UK.[1] More than 12,000 women and approximately 100 men die from breast cancer in the UK each year, making it the second most common cause of death in women after lung cancer.[1]

Types of breast cancer

An early form of breast cancer in which there is evidence of cancerous cells within the ducts (ductal cancer *in situ*) is highly localised with no spread to the surrounding breast tissue.[1] If left untreated, however, this can develop into invasive ductal breast cancer — the cause of around 70–80% of cases. Similarly, carcinomatous cells can develop in cells lining the lobules, without spread, but around 10% of breast cancers are invasive lobular cancers, and these are more common in women aged 45–55 years but rare in men.

Familial breast cancer, accounting for 5–10% of all cases, is caused by the inheritance of one of the mutated genes; *BRCA1, BRCA2, TP53* or *PTEN*.[1] Around two-thirds of women have hormone-receptor positive tumours, in which endogenous oestrogen and progesterone promote tumour growth.[1] Some cancers test positive for human epidermal growth factor receptor-2 (HER2), which also promotes cancerous growth.[1] Inflammatory breast cancer in which cancer cells accumulate in lymph channels and ducts to cause blockage and acute inflammation, is rare.[1] Paget's disease is associated with 1–2% of cases.[1] It starts with an eczema-like rash, usually affecting the skin around one nipple. In 90% of such cases an underlying mass is present, which can be invasive.[1]

Presentation

Breast cancer is most commonly diagnosed by breast screening in asymptomatic women or by self-examination. Warning signs may include any of the following:[1]

- ☐ change in size, shape or feel of breasts
- ☐ the presence of a new lumpy mass that cannot be moved independently from overlying skin
- ☐ thickening in one breast or armpit
- ☐ any puckering, dimpling or redness of the skin
- ☐ changes in the position of nipple, nipple inversion, nipple rash or discharge
- ☐ a new one-sided pain or discomfort.

The NHS Breast Screening programme is perhaps one of the most successful in Europe, saving an estimated 1400 lives each year.[2] The programme has contributed

Table 1. Staging breast cancer[3]

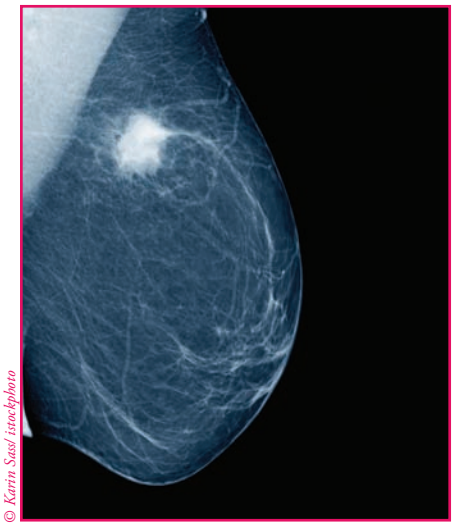
Stage	Description
I	Tumour measures <2cm. Lymph nodes in armpit unaffected. No signs that cancer has spread elsewhere in the body.
II	Tumour measures 2–5cm or lymph glands in armpit affected or both. No signs that cancer has spread further.
III	Tumour measures >5cm and may be attached to surrounding structures such as muscle or skin. Lymph glands are usually affected, but there are no signs that the cancer has spread beyond the breast or lymph glands in the armpit. This is locally advanced breast cancer that is further divided into stage IIIA, IIIB, IIIC depending on the degree of involvement with the lymph nodes or surrounding structures. Treatment may differ between each stage.
IV	Tumour is of any size, but lymph glands are usually affected and the cancer has spread to other parts of the body. This is secondary or metastatic breast cancer.

greatly to improved early detection and better treatment.[2]

Diagnosis

Investigations are usually undertaken in women who have noticed concerning changes in their breasts that cause them to consult their GP who, after examining the breasts will refer the patient to hospital or breast clinic for a full investigation. This will include a medical history and breast examination to feel for any enlarged lymph nodes at the base of the neck and armpits. Diagnostic tests include a mammogram, which is useful for finding early changes in the breasts where it may be difficult to feel a lump in women aged 50 years or more.

For younger women (particularly <35 years[1]) an ultrasound is usually preferred, because their breasts are too dense to give a clear view through mammography.[1] Ultrasound however, can determine whether the breast lump is solid or a cyst.[1]



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Subsequently, a biopsy may be taken — this may be to sample a few cells through fine needle aspiration cytology or to obtain core tissue from the lump using a larger needle biopsy and will allow a determination of malignancy of the tissue. Further scans may be carried out such as CT, MRI or PET scans if more detail is required and to check for secondaries.[1] An excision biopsy removes the whole lump for examination. Many women diagnosed with breast cancer will have surgery and various standard blood tests are carried out as part of a pre-operative screen, including:

- full blood count
- liver function tests
- calcium and alkaline phosphatase
- urea and electrolytes.

All patients should also be tested for the presence of oestrogen, progesterone and HER2-positive cells to see whether targeted therapy might be helpful. Once a diagnosis is made, the patient's cancer is staged and graded according to its progression to help decide which treatment regimen is most appropriate.

Stages and grading of breast cancer

The stage of breast cancer describes its size and whether it has spread beyond its original site. In terms of treating a patient the grade is considered less important than the stage but produces an idea of how quickly the cancer may develop and refers to the histological type of cancer cell.

Once a diagnosis is made the patient's cancer is staged and graded according to its progression to help decide which treatment regimen is most appropriate.

Staging

Stage 0 is ductal carcinoma *in situ* (DCIS) where the cancer cells are completely contained within the breast ducts and this is almost always curable with treatment. Invasive breast cancer stages progress from stage I to stage IV as indicated in Table 1.[3]

Grading

There are three main grades of breast cancer as shown in Table 2.[3]

Treatment

The treatment depends on the stage and grade of cancer (whether this is an early stage local tumour, locally advanced or metastatic), a patient's age, menopausal status, whether the cancer is oestrogen-receptor positive (ER+) or HER2+, previous treatment experience, and their fitness and wishes.[1,4] Systemic treatments should be guided by evidence-based guidelines that are reviewed regularly to incorporate current research. Where appropriate, patients should be invited to participate in well-designed clinical trials.[4] In addition to radiotherapy; therapeutic options are either surgical, pharmaceutical or both.

Surgery

Surgical treatment is the main curative modality for primary breast cancer, where

Table 2. Grading breast cancer[3]

Grade	Description
1	Low grade. Cancer cells look similar to the normal cells of the breast. They are usually slow to grow and less likely to spread.
2	Moderate/intermediate grade
3	High grade. Tumour cells look abnormal. They are more likely to grow and spread quickly.

Table 3. Main agents used in breast cancer and their specific indications

Drug (Class)	**Mechanism of action**
Cyclophosphamide (Alkylating drug)	Interferes with cell replication by damaging DNA through alkylation. **Indication:** Early and metastatic breast cancer.[6–8]
5-Fluorouracil (Antimetabolite)	Pyrimidine antagonist. Uracil analogue that interferes with RNA synthesis. Interferes with DNA synthesis by inhibiting thymidylate synthesis. **Indication:** Early and metastatic breast cancer.[8–10]
Capecitabine (Antimetabolite)	Prodrug of 5-fluorouracil. **Indication:** Combined with docetaxel in preference over single-agent docetaxel for locally advanced or metastatic breast cancer, in those where anthracycline-containing chemotherapy has failed.[11,12] Monotherapy recommended by NICE as option in locally advanced or metastatic breast cancer in those who have not had capecitabine combination therapy and after failure of a taxane and anthracycline-containing regimen or where anthracyclines are contraindicated.[11,13–16]
Gemcitabine (Antimetabolite)	Pyrimidine antagonist. DNA strand terminator. Inhibits RNA synthesis by disrupting the phosphorylation of nucleosides. **Indication:** Combined with paclitaxel in metastatic breast cancer after relapse with adjuvant/neoadjuvant chemotherapy, including an anthracycline unless contraindicated.[17] Within its licensed indication NICE recommends this combination as an option for metastatic breast cancer only when docetaxel monotherapy or docetaxel plus capecitabine are also considered appropriate.[18]
Methotrexate (Antimetabolite)	Folic acid antagonist. Inhibits dihydrofolate reductase (essential for thymidylate synthesis). **Indication:** Combined with cyclophosphamide and 5-FU for primary breast cancer with positive axillary lymph nodes, adjuvant to radical masectomy.[19] Metastatic breast cancer.[8]
Epirubicin (Anthracycline)	Intercalation with planar ring of DNA to inhibit nucleic acid synthesis and mitosis. **Indication:** Adjuvant treatment of early breast cancer combined with cyclophosphamide and 5-FU.[20]
Doxorubicin (Anthracycline)	DNA topoisomerase II inhibitor. **Indication:** Combined or monotherapy in metastatic breast cancer for patients with poor performance status.[21] (Used interchangeably with epirubicin. Cardiotoxic so avoid in patients with cardiac risk. Anthracycline monotherapy usually reserved for the frail who don't tolerate combination chemotherapy.)
Mitomycin (Anthracycline)	Alkylates and cross-links with DNA disrupting its synthesis. **Indication:** Combined or monotherapy in metastatic breast cancer.[22,23]
Mitoxantrone (Anthracenedione)	DNA topoisomerase II inhibitor. **Indication:** Metastatic breast cancer.[24]
Docetaxel (Taxane — diperpine)	Decreases presence of free tubulin by disrupting microtubule formation. Mitotic spindle formation is inhibited leading to mitotic arrest. **Indication:** Combined with doxorubicin in locally advanced or metastatic breast cancer.[24] Combined with doxorubicin and cyclophosphamide (licensed indication) recommended by NICE as option for adjuvant treatment in operable early node positive breast cancer.[25] Monotherapy in locally advanced or metastatic breast cancer after failure with chemotherapy including an anthracycline and alkylating agent.[26] Combined with trastuzumab in metastatic HER2+ breast cancer in women who have not received chemotherapy, and where anthracycline therapy is inappropriate.[24,27] Combined with capecitabine in locally advanced or metastatic breast cancer after failure of chemotherapy that includes an anthracycline.[11,27]
Paclitaxel (Taxane)	Disrupts organisation of microtubule network essential for mitosis. **Indication:** Adjuvant treatment for node positive breast cancer with an anthracycline and cyclophosphamide.[28] Initial treatment of locally advanced or metastatic breast cancer with either an anthracycline or trastuzumab.[8] Monotherapy for metastatic breast cancer unresponsive to initial anthracycline therapy or where contraindicated.[28] Within its licensed indication, paclitaxel is not recommended for the adjuvant treatment of women with early node-positive breast cancer.[29]
Trastuzumab (Humanised monoclonal antibody)	Antibody against the protein HER2. **Indication:** Early and metastatic HER2+ breast cancer.[24] NICE recommends use for adjuvant treatment of early HER2+ breast cancer given at 3-weekly intervals for a year, or until disease reccurs. Also recommended as an option in early breast cancer after surgery, chemotherapy (neoadjuvant/adjuvant) and radiotherapy.[30] Recommended and licensed in combination with paclitaxel or docetaxel (also often used with vinorelbine but not licensed) in metastatic breast cancer when anthracycline therapy is inappropriate.[8] Monotherapy recommended if received at least two chemotherapy regimens for metastatic breast cancer. Prior chemotherapy must have included an anthracycline and taxane, if appropriate. Hormonal therapy should also be included in suitable ER+ patients.[8] Licensed with an aromatase inhibitor in postmenopausal women with metastatic breast cancer, who have not received trastuzumab.[24]
Vinorelbine (Vinka alkaloid)	Inhibits tubulin polymerisation and binds to mitotic microtubules causing mitotic arrest. **Indication:** Advanced breast cancer stage III and IV, relapsing after or refractory to anthracycline chemotherapy.[31] Not recommended by NICE as first-line treatment for advanced breast cancer, but monotherapy recommended as one option for second-line or subsequent line therapy when anthracycline-based regimens have failed. The present state of evidence does not allow recommendation of the routine use of vinorelbine combination therapies, although vinorelbine is combined with trastuzumab as unlicensed therapy.[31–33]

reconstruction should be available at surgery.[4] Surgical interventions are generally either: lumpectomy, where small, localised tumours are removed along with minimal surrounding breast tissue; segmental excision, which is similar to lumpectomy but more of the surrounding tissue is removed, and mastectomy in which the whole breast is removed.[1]

Radiotherapy

Radiotherapy lowers the risk of cancer recurring, either in the remaining breast tissue or in lymph nodes that are treated.[5] Radiotherapy should be regarded as standard therapy for all women who have undergone breast conserving surgery, and considered for women who have had a masectomy.[4] Radiotherapy may also be given as neoadjuvant and adjuvant treatment, or as a sole treatment modality if surgery is inappropriate.[4]

Pharmaceutical therapies

Pharmaceutical agents, which will form the main focus of this review, include chemo-, hormonal and targeted therapies.

Chemotherapy

Chemotherapy involves using a variety of cytotoxic agents to halt tumour growth and/or destroy growing cancer cells. Chemotherapy can be given as neoadjuvant before surgery to shrink a tumour to make surgery easier/more successful, or as adjuvant after surgery to reduce the risk of disease relapse/recurrence, or for advanced disease as a palliative therapy to treat tumour spread.[1] The main classes of chemotherapies used

Table 4. Common combinations used to treat breast cancer

Combination	Evidence
CMF: Cyclophosphamide, Methotrexate, 5-FU	This traditional regimen is being replaced with anthracycline regimens which when compared to CMF, have shown increased absolute survival rates from 69% to 72% and reduced recurrence (12%).[4] This combination can be used if anthracycline therapy is inappropriate (e.g. cardiac disease).[24]
TAC: Docetaxel, Doxorubicin, Cyclophosphamide	Recommended as an option for adjuvant treatment with early node positive breast cancer.[24,25] However, sequential regimens of anthracyclines followed by docetaxel would be preferred because of their high toxicity.
Epirubicin followed by CMF **FEC:** Epirubicin, Cyclophosphamide, 5-FU **MMM:** Methotrexate, Mitoxantrone, Mitomycin **MM:** Methotrexate, Mitoxantrone **AC:** Doxorubicin, Cyclophosphamide	Adjuvant chemotherapy should include an anthracycline unless contra-indicated. Epirubicin with CMF is more effective than CMF alone.[4] Anthracycline and cyclophosphamide therapy is the standard initial therapy for metastatic breast cancer in women who have not previously received chemotherapy.[10,24]
Docetaxel/Paclitaxel (Taxanes)	Taxanes appear to be more effective than longer-established regimens using cyclophosphamide, 5-FU and doxorubicin or single-agent doxorubicin for metastatic breast cancer. They produce a better response rate and longer remission with an estimated increase in survival time of 20-25%.[4]
Single trastuzumab/ Trastuzumab + Paclitaxel	Licensed for tumours highly expressive of HER2.

for breast cancer are alkylating agents, anthracyclines, antimetabolites and taxanes. The main chemotherapeutic agents are listed in Table 3 alongside their indications specific to breast cancer and associated NICE guidance.

Common combination therapies

A combination of chemotherapy agents has been shown to reduce annual recurrence rates and overall death rates by 28% and 17% respectively.[3] Poly-chemotherapy is therefore favoured over monotherapy, especially in women aged less than 50 years and some of the common combinations used along with evidence to support this is summarised briefly in Table 4. There is insufficient evidence in women aged more than 70 years.[34]

Dosing cycles

NICE recommends that adjuvant chemotherapy for breast cancer should consist of 4–8 cycles with multiple agents, including an anthracycline (epirubicin/doxorubicin). The optimum regimen remains unclear and variations in prescribing habits exist between oncologists.[4]

Hormonal therapies

Steroid hormone-receptor positive breast cancer can be managed with hormonal therapy and the main options are tamoxifen, aromatase inhibitors (AI's) and pituitary down-regulators. Hormone antagonists are used in pre-operative or post-operative breast cancer management, or recurrences.

Tamoxifen

Tamoxifen, the oestrogen receptor antagonist, is the treatment of choice in premenopausal, perimenopausal and postmenopausal women with metastatic breast cancer.[24] Used alone or after surgery, it delays the development of metastases and has been the standard adjuvant hormonal treatment for postmenopausal women with early ER+ breast cancer when given for five years.[35] Adjuvant tamoxifen substantially improves the 10-year survival of women with ER+ breast cancer.[36]

Aromatase inhibitors for postmenopausal women

AI's, taken daily, inhibit the conversion of androgen to oestrogen in peripheral tissues. They do not inhibit ovarian oestrogen synthesis and therefore, are effective only in postmenopausal women. Their use in early ER+ breast cancer in postmenopausal women has been reviewed previously in *Pharmacy in Practice* and readers are referred to this article for further information.[37] The AI's anastrozole, exemestane, and letrozole are all licensed as adjuvant therapy for early ER+ breast cancer for postmenopausal women.[35] NICE recommends the following options for early ER+ breast cancer:[35]

- Anastrozole. Primary adjuvant therapy. Also considered for women who have already received 2–3 years of adjuvant tamoxifen.[38]
- Exemestane. Recommended after 2–3 years of initial adjuvant treatment with tamoxifen.
- Letrozole. First-line hormonal treatment and for extended hormone treatment after taking tamoxifen.

AI's also have a role in advanced breast cancer where anti-oestrogen therapy with tamoxifen has failed, as detailed in Table 5.

Table 5. Aromatase inhibitors and their indications

AI	Indication
Anastrozole	Advanced breast cancer in postmenopausal women.[38–41]
Exemestane	Advanced breast cancer in postmenopausal women whose disease progressed despite anti-oestrogen therapy.[42–45]
Letrozole	First-line treatment in postmenopausal women with advanced breast cancer.[46,47] Advanced breast cancer in postmenopausal women where tamoxifen or other anti-oestrogen therapy has failed.[48–51] Pre-operative therapy in postmenopausal women with localised hormone receptor positive breast cancer to allow breast-conserving surgery.[52,53]

Anastrozole and letrozole are at least as effective as tamoxifen for first-line treatment of metastatic breast cancer in postmenopausal women. However, it is not known whether their benefits persist in the long term.[24]

NICE recommends adjuvant chemotherapy for breast cancer should consist of 4–8 cycles with multiple agents, including an anthracycline.

Pituitary down-regulators

Goserelin (Zoladex) is the most commonly used pituitary down-regulator. It is a luteinising hormone releasing hormone (LHRH) agonist. With chronic use it inhibits pituitary LH secretion leading to a fall in oestrogen and testosterone. Goserelin is licensed for the management of advanced breast cancer in and pre- and perimenopausal women.[54]

Targeted therapies

This includes the monoclonal antibodies, trastuzumab (Herceptin) and the small molecule tyrosine kinase inhibitor lapatinib (Tykerb). Trastuzumab, which is licensed for early and advanced breast cancer, binds with the protein HER2/neu (also known as epidermal growth factor receptor-2 or erbB2 (Table 3)[8] and thereby blocks its promotion of tumour growth. Lapatinib binds to both HER2/neu receptors and to epidermal growth factor receptor-1 (erbB1) in breast tissue. Lapatinib is now licensed in the UK for metastatic disease in combination with capecitabine and is currently undergoing early clinical trials in adjuvant disease.

Trastuzumab was initially recommended for use in only advanced breast cancer by NICE.[8] Because up to 25% of cases may test positive for HER2, the absence of a licence in early breast cancer was continuously questioned in light of promising clinical trials.[55,56] This absence caused further controversy by the creation of a 'postcode lottery' where certain health authorities and hospitals would fund the treatment, which for each patient averages £21,500 PA.[8,30] Consequently, final guidance from NICE was published soon after the licence in early breast cancer was accepted by the regulatory authorities in 2006.[30]

Future research

Numerous clinical trials are underway to evaluate existing and novel therapeutic agents or management strategies for breast cancer. To illustrate the breadth of these studies a selection of some of the current clinical trials is given in Table 6.

Table 6. Some ongoing clinical trials

Carboplatin and Gemcitabine chemotherapy for breast cancer resistant to anthracyclines and taxane chemotherapy. Phase II trial. Aims to assess the effectiveness of this combination as gemcitabine is already used in combination but carboplatin is not.[57]

TACT2 trial: Comparing two weekly and three weekly epirubicin combined with either CMF or capecitabine after surgery for breast cancer. Phase III trial. Aims to assess the efficacy of accelerated treatment with the addition of capecitabine.[57]

SOFEA trial: Hormone therapy for advanced breast cancer. Phase III trial. Involves fulvestrant which down-regulates oestrogen receptors and is an oestrogen antagonist. Aims to assess superiority of fulvestrant vs. anastrozole, fulvestrant vs. placebo and exemestane in advanced breast cancer unresponsive to AI therapy.[57]

TNT trial: Triple Negative breast cancer. Phase III trial. Carboplatin is compared to docetaxel for metastatic or recurrent locally advanced ER-, PR- and HER2- breast cancer.[57]

ACTION trial: Adjuvant chemotherapy in older women. Phase III trial. Aims to assess adjuvant chemotherapy in women aged more than 70 years, and whether accelerated therapy with GCSF support will not cause undue toxicity in this group.[57]

SOFT trial: Suppression of ovarian function. Phase III trial. Aims to assess efficacy of tamoxifen alone, tamoxifen and ovarian ablation, and exemestane and ovarian ablation.[57]

PERSEPHONE trial: Duration of trastuzumab. Phase III trial. Aims to assess whether women with early breast cancer can safely have trastuzumab for 6 months instead of 12 months to help lower the risk of cardiac damage.[57]

ASBO study: Phase II trial. Single-arm trial of pertuzumab (HER2 dimerisation inhibitor) and trastuzumab in HER2+ metastatic breast cancer. Promising results recently show patients whose disease progressed with trastuzumab benefited with combined monoclonal antibody therapy. This combination is also being evaluated against chemotherapy in the CLEOPATRA trial.[58]

TBP study: Phase III trial. Aims to assess trastuzumab treatment in patients with HER2+ metastatic breast cancer requiring subsequent lines of treatment. Recent results showed a significant improvement by continuing on trastuzumab in combination with oral capecitabine compared with capecitabine alone.[59]

Summary

Chemotherapy treatment options for breast cancer offer a good degree of choice of single agents or combinations, tailored to the type of cancer and its degree of progression. Adjuvant chemotherapy should be offered in 4–8 cycles of multiple-agent chemotherapy, which should include anthracyclines. If anthracycline therapy has failed or is contraindicated, capecitabine is an option for locally advanced or metastatic breast cancer. Vinorelbine monotherapy or gemcitabine and paclitaxel are other options in metastatic breast cancer.

Taxanes are recommended as an option for advanced breast cancer where initial chemotherapy with anthracyclines has failed. They are not licensed for adjuvant treatment in early breast cancer, but are combined with trastuzumab in metastatic breast cancer where anthracycline therapy has failed. Trastuzumab is also used as monotherapy in early and metastatic breast cancer.

All women with hormone receptor-positive tumours should be offered hormone treatment for five years after primary therapy. This is likely to involve tamoxifen, or an AI plus ovarian ablation or an LHRH agonist for pre-menopausal women.

Clinical guidelines on the diagnosis and treatment of early and advanced breast cancer are currently pending from NICE. The clinical trials mentioned in this overview of breast cancer management represent a selection of the main trials in progress, which will no doubt contribute to the evidence base for the development of future breast cancer management strategies. ✣

Declaration of competing interests

The author declares she has no competing interests.

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