piratory lesions, malignancies, leukaemia, lymphoma, lung cancer and other neoplasms such as sarcomas.22

Localised intraoperative radiation therapy (IORT) treats only the operation area with electrons from a mobile linear accelerator (of which there are only 9 licensed by the Food and Drug Administration (FDA) in the USA).

A range of techniques are being tried using brachytherapy, and tagging cancer cells with a radioactive isotope is another avenue of investigation. Dr Gary Freedman23 from Philadelphia reported on an analysis of 2 700 women who had whole-breast irradiation and noted that after 15 years the incidence of recurrences in the original tumour site nearly equalled the incidence in the rest of the breast (9% and 7%).24 In other words the jury deciding on the value of partial breast irradiation will need to sit for a long time yet.

The treatment is not suitable for all patients, for example women in the 1st and 2nd trimester of pregnancy because of radiation scatter on the fetus, and in cases of true multicentricity with 2 or more tumours in the breast, diffuse indeterminate or malignant calcification in the breast and previous irradiation to the breast, involved margins despite wide excisions, large breast size, family history of breast or ovarian cancer implying a familial genetic defect, and collagen vascular disease.

A recent publication from centres in Villejuif and Chile showed that breast-conserving surgery in young women under 40 years of age shows a 4-fold more common development of late local recurrence in the treated breast compared with mastectomy.25 This may be due to the presence of morphological success, genetically pre-programmed cells, which previously could only be suspected in the presence of significant family history of breast cancer. Alternative procedures should be offered to patients in whom the breast-conserving option is contraindicated or refused.

These include skin-sparing mastectomy and total mastectomy with immediate reconstruction using parenchymal flaps, pedicle flaps, free flaps and trans-abdominal rectus abdominis mobilisation (TRAM) flaps. The TRAM flap was developed as a result of patient insistence — German women with somewhat larger and more pendulous breasts refused to have surgery on the healthy breast to match the reconstruction.

Axillary lymph nodes

Involvement of the axillary lymph nodes is the best guide to the likelihood of occult systemic metastases and the use of adjuvant systemic therapy. The number of involved nodes is prognostic; if more than 4 nodes are positive, this is an indication for therapy to the gland fields and chest wall for improved local control.

A properly dissected axilla should not be irradiated to avoid the distressing and incurable complication of arm lymphoedema.

Sentinel node biopsy with frozen section or cytological examination will enable the decision regarding the full axillary dissection to be taken at the time of breast surgery, and if negative avoid the unnecessary more radical dissection.

Other criteria can also be used instead of the axillary node status to indicate the need for adjuvant systemic therapy. These are: (i) the size of the primary tumour; (ii) a negative oestrogen receptor (ER) assay on the primary tumour; (iii) over-expression of the HER-2-neu gene; (iv) angio-invasion (lymphatic or vascular); and (v) extensive neo-angiogenesis around the primary tumour.

Screening mammography and the early use of adjuvant systemic therapy are the only factors that have led to an improvement in the survival figures for breast cancer.

Adjuvant systemic therapy

In 1802 a medical staff meeting at St Bartholomew's Hospital in London discussed the question of breast cancer being a local or a systemic disease. Present were John Abernethy, John Hunter’s pupil and successor at St Bartholomew’s Hospital; Matthew Baillie, his nephew; his brother-in-law Everard; and Robert Willen, founder of British dermatology.26 When first seen at that time breast cancer certainly was a systemic disease, as it is in the majority of cases when first seen in South Africa today.

Hormonal adjuvant systemic therapy

In 1836 Astley Cooper drew attention to cyclic variation in tumour size related to the menstrual cycle, and associated nulliparity with the incidence of breast cancer.27 These clinical features and slow growth with cell differentiation were the only factors to predict a response to hormone manipulation.

The move from empirical therapy to the world of molecular biology was heralded by the 1967 report from Jensen et al.28 describing specific binding of radioactive oestrogen to those specimens of breast cancer with a favourable clinical response. The concept of receptor proteins for oestrogens and progesterones and indeed for all hormones was developed. In the 1980s A. Walpole, the head of the fertility control programme at Imperial Chemical Industries, while looking for a post-coital ‘morning-after’ pill, discovered tamoxifen, an oestrogen antagonist and agonist.29 This drug proved to be a highly active and relatively safe therapeutic agent in ER-positive breast cancers. It is also successful in the prevention of breast cancer.

New anti-oestrogen drugs have been developed and an aromatase inhibitor, anastrozole, has recently been shown to be more effective than tamoxifen in the adjuvant setting; because of a lack of crossover resistance, it can be used after tamoxifen failure or in patients who develop thromboembolism.

Hormone replacement therapy

HRT, the most efficient treatment of menopausal symptoms, has not lived up to its initial reputation for preventing heart disease, strokes, etc. and it is associated with a small increase in the incidence of breast cancer with long-term use.

Chemotherapy

Trials in patients with advanced disease, treatment of which is essentially palliative, indicate the possibilities for use in the adjuvant setting where survival may be increased. In 1977 Fisher et al.30 reported on the first of a series of trials using surgery followed by early treatment with thio-tepa, which improved survival. Bonadonna et al.31 'jumped the gun', to use Fisher’s phrase, and reported the updated results with the use of CMF (cyclophosphamide, methotrexate, fluoro-uracil). The responses, which occur in only 30 - 50% of patients, are genetically controlled.

Immunology

The use of immunohistochemistry for the detection of ER and progesterone receptor (PGR) in tissue specimens has made the process much easier but there is still the problem of consistent standards in South African laboratories. Some are accurate and others not. The first practical application of immunogenetics in the management of breast cancer appeared recently in the use of the HER-2-neu gene to guide
the use of herceptin, an antibody to breast cancer. This gene must be over-expressed at a level of +3; if necessary a fluorescent in situ hybridisation (FISH) test can be used.

What have we achieved during the last 50 years?

1. Longer disease-free survival: (i) improved prediction of who will develop breast cancer; (ii) earlier diagnosis with mammographic screening; and (iii) more effective systemic adjuvant therapy.

2. Improved local control: (i) linear accelerator and simulator; (ii) intra-operative electron therapy?

3. Less mutilation: (i) needle biopsy; (ii) breast-conserving surgery; (iii) immediate reconstruction; and (iv) oncoplastic surgery.

4. Individualisation of treatment: (i) this is the ultimate objective of treatment, and has been partially achieved; (ii) better patient education through the Internet, lay press celebrity pitches, and patient advocacy groups; and (iii) a reduction in the paternalistic attitude of doctors, and patient involvement in decision making.

We have come a long way in the last 50 years, and have a much longer way to go. When the late Professor Eugene Dowdle from Cape Town was asked at a breast cancer symposium: ‘Has immunology a future in the treatment of breast cancer?’ he gave a characteristically swift and pertinent reply, ‘Immunology will always have a great future’.

REFERENCES


