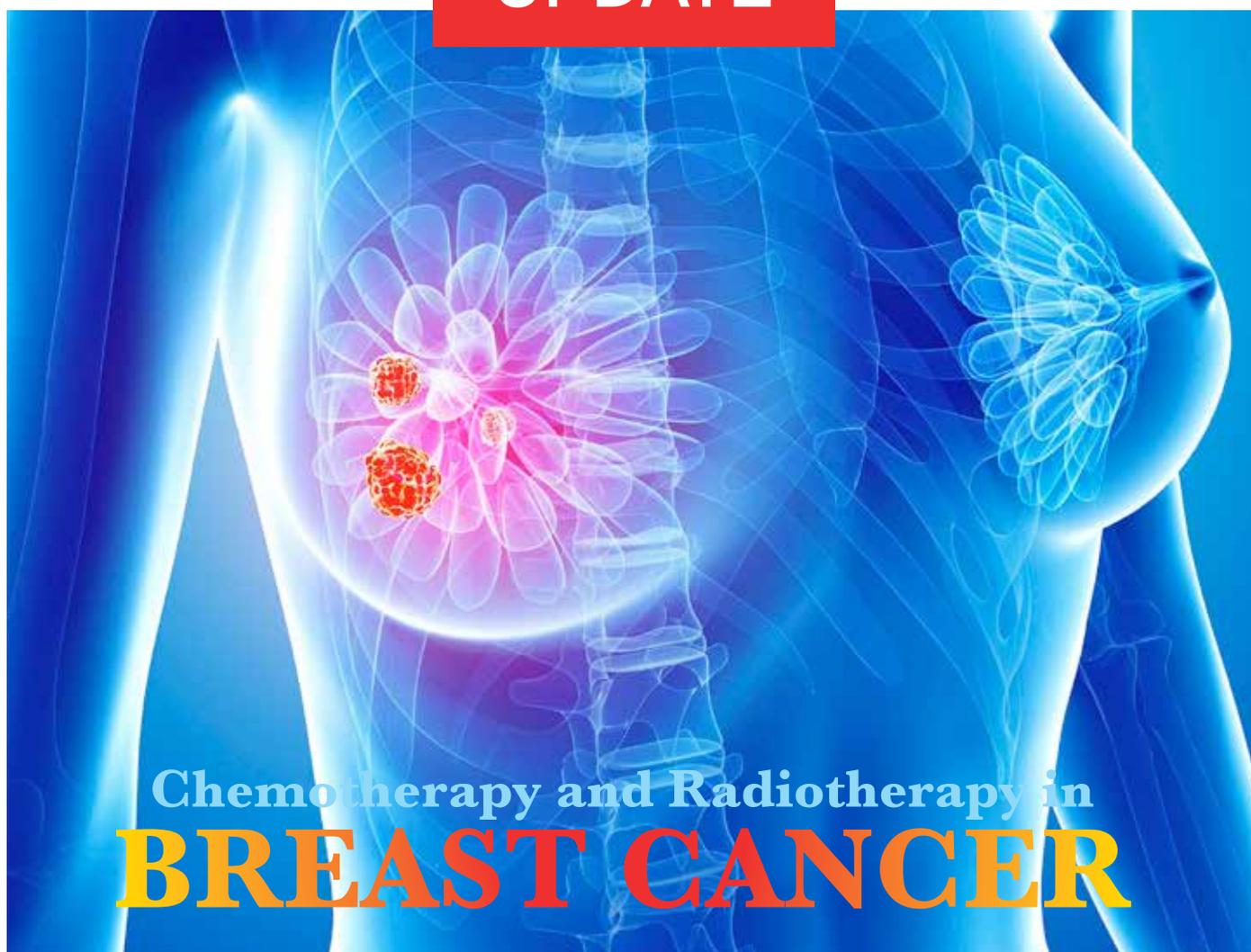


SURGICAL UPDATE



Chemotherapy and Radiotherapy in **BREAST CANCER**

Chemotherapy is a vast and complicated field with many factors influencing whether a patient should have chemotherapy, and if so, what regime?

Every patient and tumour are different and so treatment needs to be tailored to the individual. Although the oncologist gives the final recommendation and administers the therapy, it is often the doctor who makes the initial diagnosis of cancer, or the family practitioner who has suspected the diagnosis, who will need to answer a patient's many questions prior to them seeing the oncologist.

This update seeks to give some of the general principles of chemotherapy and radiotherapy and summarise recent developments as to who should get these treatments, what agents are used and what to expect in terms of outcomes.

A few explanatory notes are required to help explain the various treatment pathways.

Staging: in breast cancer refers to size of tumour, involvement of regional lymph nodes, and presence or not of spread to other organs.

Stage I and II – includes small tumours with or without involvement of less than 3 axillary nodes, or a larger tumour (>5cm) with no lymph node involvement

Stage III – includes small tumours with extensive lymph node involvement, a large tumour with involved lymph nodes, or a tumour that is infiltrating the muscle of the chest wall

Stage IV – includes a tumour of any size that has spread to other organs (metastases), e.g. bones, lungs, liver, brain

Grade:

This varies from Grade 1 where the cells still resemble normal breast tissue cells and are slow-growing, to Grade 3 where the cancer cells are faster growing and more likely to spread to other tissues in the body (metastasize).

Ki - 67:

A protein associated with cellular proliferation and tumour growth. A level > 20 % may indicate an increased incidence of tumour recurrence.

Endocrine therapy :

50 – 70% of breast cancers require estrogen and progesterone to grow. If the tumour cells are Estrogen receptor (ER) or Progesterone Receptor (PR) positive, then a hormone receptor blocker such as tamoxifen, or prevention of production of oestrogen by an Aromatase Inhibitor (AI), e.g. Arimidex or Femara will decrease the risk of recurrence of breast cancer and improve long term survival from a breast cancer point of view.

The 15 year follow up in the EBCTCG (**Fig 1**) shows the recurrence and death rates to be significantly decreased in the group taking Tamoxifen for 5 years compared to the control group. Recent trials have shown that there may be a

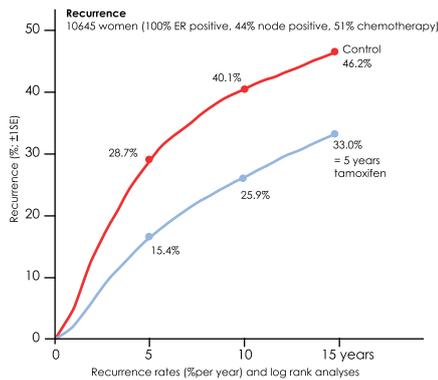
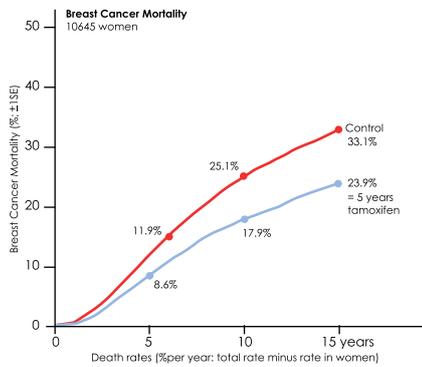


Fig 1: Early Breast Cancer Trialists' Collaborative Group (EBCTCG) Lancet 2011

further survival benefit by increasing the duration of Tamoxifen to 10 years.

Post menopausal patients may be started on an AI or alternatively be started on Tamoxifen and then converted to an AI later. Those post-menopausal patients with low risk tumours will start with Tamoxifen.

One of the side effects of an AI is osteoporosis. Patients on AI's need to follow a healthy diet, do weight-bearing exercise and take vitamin D and calcium supplements to maintain bone health. Other side effects include an increase in cholesterol and muscle and joint pain.

Side effects of Tamoxifen include hot flashes, vaginal discharge and a slightly increased risk of DVT, stroke and endometrial (uterine) cancer.

HER 2 status:

Assesses whether the tumour cells are expressing too many of this growth factor's receptors. It is present in 15% to 20% of breast cancers. It is associated with increased growth rates and had a worse prognosis than HER 2 negative tumours until the advent of HER 2 receptor blockers such as Trastuzumab (Herceptin).

The graph (See Fig 2) demonstrates a significant improvement in disease-free survival and overall survival in the group of patients who received Herceptin in addition to chemotherapy when they had a HER2 + breast cancer.

Luminal A tumour:

These tumours have the following characteristics: strongly ER and PR positive, HER 2 negative, have a low Ki-67 and are typically slow-growing. They are less likely to respond to chemotherapy which is more effective with fast-growing cells, and therefore only require endocrine therapy after surgery. Only if the patient has a very large tumour or several involved nodes then they may benefit from chemotherapy even though their tumour is classified as a luminal A tumour.

Luminal B tumour:

These tumours are ER positive, PR negative or weakly positive, HER 2 positive or negative and have a high Ki-67 (> 20%). They tend to grow more quickly than luminal A tumours and are therefore more likely to benefit from chemotherapy as well as hormonal therapy and treatments targeting the HER2 receptor if positive.

Triple negative breast cancer:

These tumours are negative for ER and PR receptors and are HER2 negative. These tumours tend to be faster growing, have a poorer prognosis and will require chemotherapy unless they are very small.

Genomic testing:

These tests aim to more accurately predict the biological aggressiveness of a tumour by looking at several groups of genes linked to growth and ability of the tumour to metastasize. Oncotype Dx and MammaPrint are the 2 best validated models. Both are found to be accurate prognostic indicators and predictors of breast cancer relapse.

Oncotype Dx provides a recurrence score (RS) based on a 21 gene panel associated with cancer prognosis. The test has been shown to provide predictive and prognostic information in ER positive, lymph node negative tumours by providing an RS value which varies from 0 to 100, and predicts the risk of ten year recurrence.

Low risk (RS <15): low risk of recurrence and therefore little benefit from chemotherapy.

Intermediate risk (RS 16-25): may or may not benefit from chemotherapy; further discussion required. Patients younger than 50 years of age may benefit from chemotherapy if they fall into this group.

High-risk (RS >25): high risk of recurrence and therefore benefit from chemotherapy.

Adjuvant chemotherapy:

is chemotherapy administered after surgery for early breast cancers with the goal of trying to eradicate any tumour cells that may have spread to other sites in the body and which cannot be detected on imaging. If untreated these may subsequently present as metastases, and are the biggest determinant of long term survival in any cancer.

Neoadjuvant chemotherapy:

this is chemotherapy administered prior to surgery in certain situations - for large tumours or tumours fixed to the chest wall to render the tumour operable

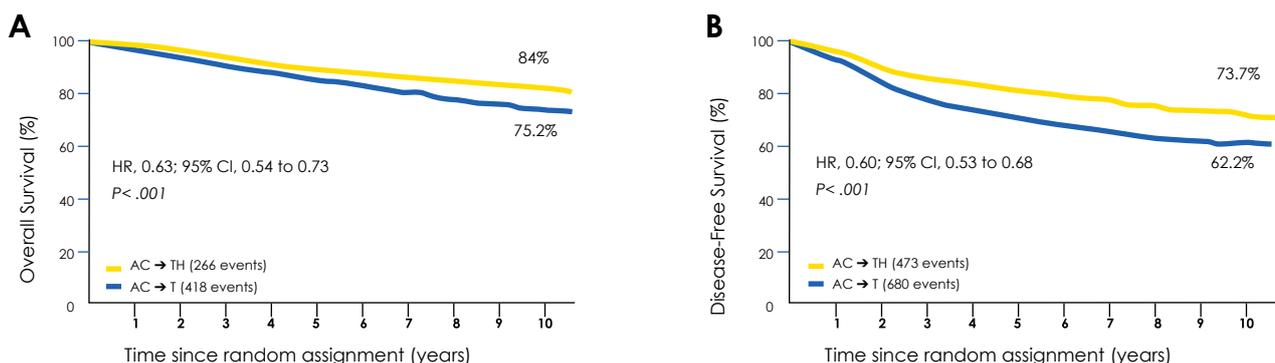


Fig 2: National Surgical Adjuvant Breast Project (NSABP) ; J Clin Oncology 2014

- might enable a lumpectomy (wide local excision) rather than removing the entire breast
- tumour has spread to the axillary nodes and patient clinically has a large tumour burden
- enables evaluation of tumour response to therapy - helps clarify best choice of chemotherapy agent
- high grade tumours (Grade 3)
- triple negative tumours
- HER2 positive tumours

Effectiveness of chemotherapy

In older trials patients receiving chemotherapy show a 16 to 24% decrease in mortality at 10 years compared to patients not receiving chemotherapy.

These trials were done with the older regimes of chemotherapy which included cyclophosphamide, methotrexate and 5-fluorouracil (CMF), and later an anthracycline e.g. an adriamycin-based regime. Outcomes of newer regimes which use adriamycin and cyclophosphamide (AC) followed by a taxane such as paclitaxel, show at least a 10% improvement in 10 year survival compared to older regimes.

The new regimes should decrease 10 year mortality in breast cancer patients by 30 to 35%. This however is a relative benefit and is different for different tumours and patients.

A useful guide that helps to illustrate which patients will have a benefit from

the above treatments is Predict Online, a readily available tool that looks at a patient's age at diagnosis, tumour size and nodal status, hormone receptor status, HER2 status, tumour grade and Ki 67 status .

5 and 10 year survival figures are then given for surgery alone compared to surgery plus the other modalities of treatment if indicated.

A few examples follow:

Patient 1 (40 yrs) 15mm tumour; Grade 3; node negative; Ki 67 high; triple negative

- 10 year survival with surgery alone - 81%
- 10 year survival with surgery plus chemotherapy - 90%
- Therefore 9 more women with a similar tumour will survive at least 10 years due to the addition of chemotherapy

Patient 2 (65 yrs) 15mm tumour; HE2 negative; Grade 1; node negative; Ki 67 low; ER positive

- 10 yr survival with surgery alone - 88%
- 10 yr survival with surgery plus hormonal therapy - 89%
- 10 year survival with surgery + hormonal + chemotherapy - 90%
- The benefit of adjuvant therapy is minimal and probably outweighed by the side effects of treatment

Patient 3 (40 yrs) (See Fig 3) 50 mm tumour; Grade 3; node positive; Ki 67 high; ER negative; HER 2 positive

- 10 yr survival with surgery alone =27%

Overall Survival

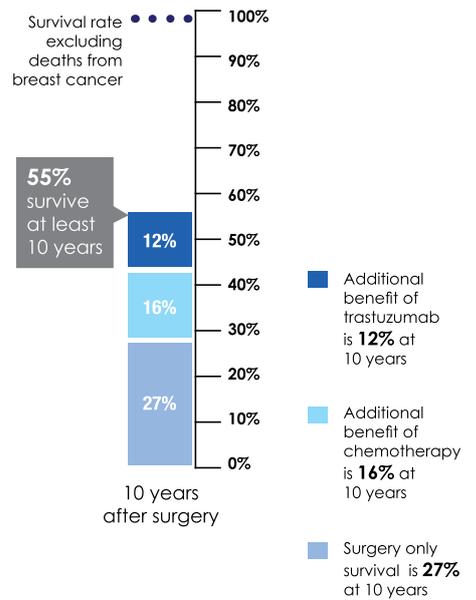


Fig 3: Predict Online for Patient 3 These results are for women who have had surgery and predict the survival at 10 years based on inputs of treatment selected.

- 10 yr survival with surgery + chemotherapy =43%
- 10 yr survival with surgery + chemotherapy + Herceptin =55%
- 32 more women will survive at least 10 years with addition of chemotherapy, and 28 women will survive at least 10 years with the addition of chemotherapy and Herceptin

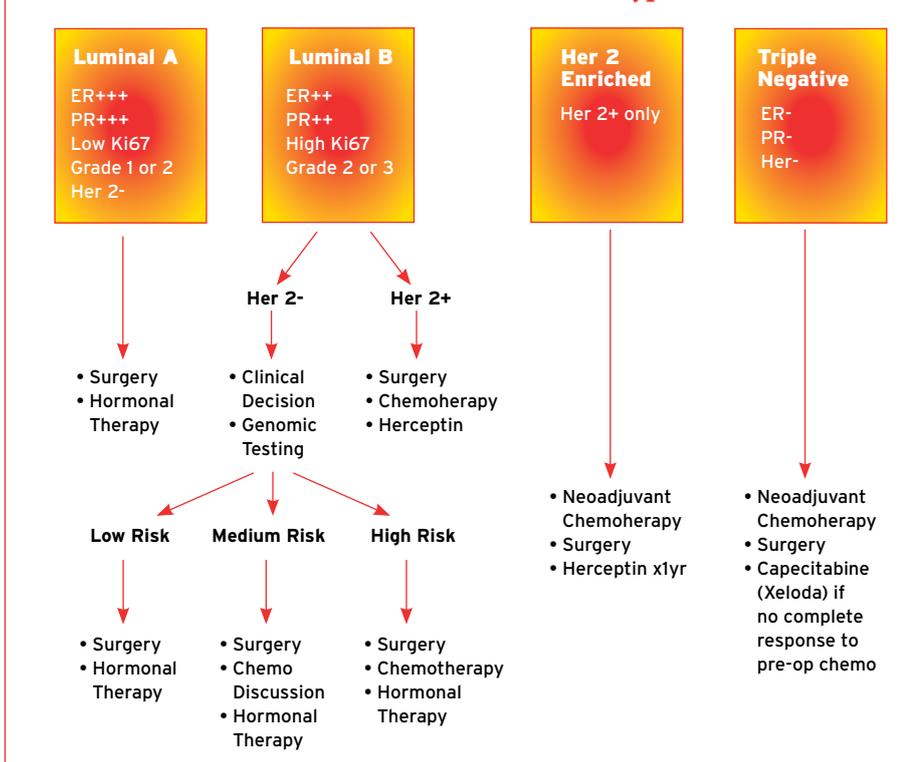
The use of Predict has been validated in large studies in several countries. It looks at many of the important factors in breast cancer prognosis but cannot include all factors such as a patient's other medical issues or ability to tolerate treatment, and does not yet include results from genomic testing. It therefore is one of the guides to determining the best therapy for the individual.

How is chemotherapy administered

With the more frequently used regime of an anthracycline + cyclophosphamide (AC) followed by a taxane such as paclitaxel, the first 2 agents are administered intravenously every 3 weeks for 4 cycles, followed 3 weeks later by a weekly dose of paclitaxel given intravenously for 12 weeks. The AC usually requires the whole morning whereas the Paclitaxel requires about one and a half hours. For the first 2 to 3 doses of Paclitaxel the infusion will take longer and an antihistamine is given to help prevent a possible allergic reaction.

This induces some drowsiness and so one may need a lift home. If there is no sign of an allergic response, the

Treatment Guidelines Based on molecular subtypes of breast cancer



antihistamine doses are adjusted so one can drive home oneself if needed usually.

For those considered not able to tolerate the above chemotherapy, particularly anthracyclines in patients with a cardiac condition, then a taxane with cyclophosphamide every 3 weeks for 4 cycles, or the traditional regime of CMF might be used and would also be given intravenously every 3 weeks, but over a period of 3 to 6 months.

Side effects:

Hair loss

Due to anthracyclines, cyclophosphamide and the taxanes - paclitaxel or docetaxel. This occurs from about 2 to 4 weeks. The hair loss is temporary and will return 3 to 6 months after finishing chemotherapy. Attempts to reduce hair loss have included scalp cooling (application of a closely fitting cap cooled by chilled liquid during the chemotherapy). The cooling cap has shown mixed results, makes the patient feel cold and frequently gives a headache.

Nausea and vomiting

Variable. Not everybody gets this. The aim is prevention, so one or more medications are given before (especially if an episode has happened before) or as soon as the symptoms start. This problem has been managed more successfully in recent years.

Neuropathy

May occur with taxanes. Symptoms usually in hands and feet - numbness burning or tingling, sensitivity to cold or heat. Most symptoms resolve once treatment is stopped. If severe, the dosage may need to be reduced or treatment stopped. High-dose vitamin B6 and immersing hands and feet in cold water during administration of the chemotherapy may be helpful.

Hand - foot syndrome

May occur with anthracyclines or capecitabine (Xeloda). These can cause irritation of the palms of the hands and the soles of the feet with numbness, tingling and redness. The skin may blister leading to peeling. Symptoms gradually get better when the drug is stopped or the dosage is lowered.



Radiotherapy Planning requires a CT scan. Each treatment session takes about 5 minutes.

Fatigue and “Brain Fog”

This is fairly common with the AC part of chemotherapy. It may last for a week to 10 days post the chemotherapy session. It is variable in its effect but may make it difficult to work during these 3 months of treatment.

Radiotherapy:

Radiotherapy is given where there is a high risk of recurrence in any residual breast tissue, the chest wall or the axillary or supraclavicular nodes.

These include:

- Post wide local excision. Long term studies show that this gives the same result as a mastectomy
- 4 or more axillary nodes containing malignant cells
- Nodes with extracapsular extension
- 1-3 positive nodes with another high risk feature for local recurrence (Grade 3, ER – cancer, young patient, bigger tumour; lymphovascular invasion)
- Tumour > 5cm
- T4 tumour; i.e. tumour has spread into the muscle, and/or into the skin

Radiotherapy is done as an outpatient once surgical wounds have settled, or following chemotherapy. It should be started at the latest by 12 weeks post-

operatively, but ideally sooner. It is administered every weekday for 3 to 6 weeks. Planning requires a CT scan. Each treatment session takes about 5 minutes. No sedation is required and there is no pain or nausea. Patients should be able to work during this time and are able to drive.

Side effects include skin changes, a redness similar to a sunburn may occur. Some patients may feel fatigued. Long-term there may be firmness of the skin and the breast if radiotherapy is being given after a lumpectomy. In a few patients a transient cough from lung irritation may occur and infrequently patients develop fatigue which resolves after the radiation has finished.

Advances in equipment and techniques have lessened the risk of affecting the cardiac muscle.

Summary

- The treatment of breast cancer has evolved considerably.
- Deciding who will really benefit from chemotherapy, endocrine therapy and radiotherapy has been better defined and is an ever-evolving field.
- Treatment types, dosages and durations of therapy have led to significant improvements in 5- and 10-year survival.
- Some side effects have been lessened and others better managed.

