Integrated Care for Breast Cancer

Latest chemotherapy, radiotherapy & hormonal therapy approaches in early breast cancer

Dr Emma Staples
Individualised Treatments

The three major treatments for breast cancer are surgery, radiotherapy and drug therapy.

No one treatment fits every patient and combination therapy is usually required to maximise cure and minimise toxicity.

The choice of treatments is determined by many factors, including patient age, menopausal status, the type of cancer, its stage, grade and receptor status.
Breast cancer treatments are defined as local or systemic

- Surgery and radiotherapy are considered local treatments because they directly treat the tumour, breast & lymph nodes. The aim is to control local disease.

- Drug treatment is termed systemic treatment as it affects the whole body and includes chemotherapy, hormones and targeted therapies such as herceptin. Its primary aim is to reduce distant relapse.

- Surgery is usually the standard initial treatment but occasionally chemotherapy or hormone therapy may be used first (neo-adjuvant or primary treatment)
Adjuvant Therapy

- Adjuvant therapy refers to ‘additional treatment’ given after surgery where all detectable disease has been removed, but where there remains a statistical risk of relapse due to occult disease.

- Oncologists use statistical evidence to assess the risk of relapse along with the known benefits and risks of treatment before recommending specific adjuvant therapies.

- Because treatment is essentially for a risk, rather than provable disease it is accepted that a proportion of patients who receive adjuvant therapy will already have been cured by their primary surgery.
Adjuvant Therapy Decision Making

- Estimate risk for recurrence
- Estimate improvement in outcome with adjuvant therapy
- Balance toxicity/benefit for the individual patient.
Creating a treatment plan: Individual Risk of Recurrence

• Age
• Size of tumour (T<2cm, 2-5cm, 5+cm)
• Grade of tumour (G1, G2, G3)
• Nodal Status (N0, N1-3, N4+)
• ER/PR Status (ER+ve better prognosis)
• Her2 status (Her+ve poorer prognosis)
• General Health
Adjuvant! Online

- Adjuvant! Online assists healthcare professionals and patients with early stage breast cancer to discuss the risks and benefits of adjuvant therapy after surgery.

- It presents estimates of the risk of cancer-related mortality or relapse, which can be used in consultations.

- Doctor and patient can use the tool together to decide on the most appropriate adjuvant treatment.
Adjuvant Online!

Adjuvant! for Breast Cancer (Version 8.0)

**Patient Information**
- Age: 66
- Comorbidity: Average for Age
- ER Status: Positive
- Tumor Grade: Grade 3
- Tumor Size: 2.1 - 3.0 cm
- Positive Nodes: 0
- Calculate For: Mortality
- 10 Year Risk: 24

**Adjuvant Therapy Effectiveness**
- Horm: Tamoxifen (Overview 2000)
- Chemo: 1st Generation Regimens

**No additional therapy:**
- 61.7 alive in 10 years.
- 21.9 die of cancer.
- 16.4 die of other causes.

**With hormonal therapy:** Benefit = 5.8 alive.

**With chemotherapy:** Benefit = 1.5 alive.

**With combined therapy:** Benefit = 6.8 alive.

[Buttons: Print Results PDF, Access Help and Clinical Evidence, Images for Consultations]
Adjuvant Online!

Adjuvant! for Breast Cancer (Version 8.0)

Patient Information
- Age: 46
- Comorbidity: Average for Age
- ER Status: Positive
- Tumor Grade: Grade 3
- Tumor Size: 2.1 - 3.0 cm
- Positive Nodes: 0
- Calculate For: Mortality
- 10 Year Risk: 24 Prognostic

Adjuvant Therapy Effectiveness
- Horm: Tamoxifen (Overview 2000)
- Chemo: 1st Generation Regimens
- Hormonal Therapy: 32
- Chemotherapy: 30
- Combined Therapy: 52

No additional therapy:
- 73.4 alive in 10 years.
- 23.6 die of cancer.
- 3.0 die of other causes.

With hormonal therapy: Benefit = 6.8 alive.

With chemotherapy: Benefit = 6.3 alive.

With combined therapy: Benefit = 11.4 alive.
66yrs ER-
Breast Cancer Chemotherapy

• Chemotherapy is usually offered to patients with a 10yr breast cancer related mortality of >10% who estimated absolute benefit from chemotherapy is >3%.

• NICE guidance recommends that chemotherapy after surgery for breast cancer should consist of 4 to 8 cycles of a combination of drugs, including an anthracycline.

• Commonly used regimes are FEC, AC, E-CMF
Taxanes

A review of chemotherapy trials in 2009 showed that adding a taxane to standard chemotherapy further reduces the risk of the cancer coming back.

On the basis of these trials taxanes containing regimes are offered to women at high risk of relapse.

This comes at the expense of added toxicity so patients must be carefully selected and appropriate supportive treatments given.
The Future: Multi-gene Assay tests

Traditional methods of estimating recurrence are being supplemented by multi-gene assay tests which give a genetic fingerprint of an individual tumour.

One such test is the Oncotype Dx which measures 21 genes.

The 16 active genes are associated with cell proliferation, cellular invasion & oestrogen activity. 5 reference genes ensure the test has not been contaminated.
Oncotype Dx

Predicts the risk of disease recurrence at 10 years in terms of a recurrence score (RS) between zero and 100.

It is intended for use in ER positive, node negative tumours.

This more accurate prognostic and predictive information improves the targeting of adjuvant chemotherapy.

It has been validated in retrospective studies & is currently being validated in prospective trials.

<table>
<thead>
<tr>
<th>Recurrence Score</th>
<th>Low Risk</th>
<th>Intermediate Risk</th>
<th>High Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;18</td>
<td>6.8%</td>
<td>14.3%</td>
<td>30.5%</td>
</tr>
<tr>
<td>18-30</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;30</td>
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</table>
Trastuzumab (Herceptin) in Her-2 overexpressing breast cancer

The HER receptors are proteins that are embedded in the cell membrane they regulate cell growth and survival.

HER2 is over-expressed in approx 20% of breast cancers, this causes breast cancer cells to reproduce uncontrollably.

Trastuzumab is an antibody that binds selectively to the HER2 protein disabling it so the cells no longer reproduce

This increases the survival of people with breast cancer.
3.4

Distant Disease-Free Survival in Patients Treated with Trastuzumab plus Chemotherapy versus Chemotherapy Alone

Trastuzumab (n = 1,672; 96 events)
- 90.4%
- 89.7%

Control (n = 1,679; 193 events)
- 81.5%
- 73.7%

Patients free of distant recurrence (%)

Years after randomization

$p < 0.0001$
Hazard ratio, 0.47

9 weeks of adjuvant Herceptin may be as effective as 1 year in the adjuvant setting!

No cardiac toxicity was observed in the trastuzumab-treated patients.

Tremendous economic implications.

Persephone trial (12 vs 6 months) currently recruiting in UK.
Chemotherapy Summary

• The decision to proceed with systemic chemotherapy is a carefully balanced decision based on assessment of risk of recurrence, expected benefit of treatment and toxicity.

• In post-menopausal women with ER + tumours and a low/moderate risk chemotherapy offers little benefit over hormone therapy alone.

• Chemotherapy is generally discussed with patients who have a 10yr breast cancer mortality of >10% and an expected survival benefit >3%.

• Standard treatment for node-negative women who require chemotherapy is 4-8 cycles of an anthracycline containing regime with appropriate support.

• Taxanes should be offered to women with node-positive disease.

• We are currently overtreating a large proportion of women genetic profiling of tumours will hopefully help to refine recurrence risk in individual women and may also indicate which chemotherapy regimes will be of most benefit.

• Adjuvant Herceptin for 1yr should be added to chemotherapy in women with HER 2 positive breast cancers >1cm however shorter durations of treatment are likely to be as effective and are currently under investigation.
Hormonal Therapy

• Approx 75% of breast cancers express ER+/-PR receptors and are therefore stimulated to grow by the female hormones oestrogen and progesterone.

• This means that drugs or treatments that block the effects of hormones, or lower the levels of oestrogen and progesterone, can be used to treat some types of breast cancer.

• There are three types of hormone therapy; tamoxifen, aromatase inhibitors eg anastrazole, letrozole & exemestane and pituitary down regulators eg Zoladex.

• Tamoxifen can be used in pre & post menopausal women but Aromatase inhibitors only work in post-menopausal women (no menstrual period for at least 12months prior to diagnosis)
Anti-Oestrogens
Mechanism of Action

Oestradiol binds to the oestrogen receptor activating oestrogen response elements (EREs) upstream of oestrogen-responsive genes including those responsible for cell proliferation.

Tamoxifen competes with oestradiol for ER binding.
Aromatase inhibitors reduce the synthesis of oestrogens from their androgenic precursors.
Tamoxifen

Approximately one-quarter of all newly diagnosed early-stage breast cancers occur in pre- or perimenopausal women.

Tamoxifen is the only hormonal agent currently available for adjuvant therapy in this population.

The Early Breast Cancer Trialists’ Collaborative Group (EBCTCG) demonstrated that adjuvant tamoxifen therapy yields substantial benefit in both younger and older women when compared with no therapy, irrespective of the use of chemotherapy and tumour characteristics.

Figure 2: Benefits of Adjuvant Tamoxifen - Early Breast Cancer Trialists’ Collaborative Group study shows that adjuvant tamoxifen x 5 years improves disease-free (Left) and overall survival (Right) with “carry-over” benefits to 15 years. SE = standard error.
Aromatase Inhibitors

There has been great interest in the benefits of aromatase inhibitors in breast cancer for the last 10 years.

Several trials have evaluating the value of third-generation aromatase inhibitors in postmenopausal women with hormone receptor-positive, early breast cancer.

These trials have included different patient populations and different designs and have featured either upfront therapy, sequential therapy entailing a switch to aromatase inhibitors following initial tamoxifen use for 2–3 years, or extended therapy continuing after completion of 5 years of tamoxifen use.
<table>
<thead>
<tr>
<th>Trial</th>
<th>Median follow-up, mo</th>
<th>Aromatase inhibitor</th>
<th>Study design*</th>
<th>Disease-free survival benefit</th>
<th>Overall survival benefit</th>
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<tbody>
<tr>
<td>ATAC&lt;sup&gt;12&lt;/sup&gt;</td>
<td>100</td>
<td>Anastrozole</td>
<td>Upfront</td>
<td>Yes (HR, 0.90; ( P = 0.025 ))</td>
<td>No</td>
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<tr>
<td>BIG 1-98&lt;sup&gt;13&lt;/sup&gt;</td>
<td>51</td>
<td>Letrozole</td>
<td>Upfront</td>
<td>Yes (HR, 0.82; ( P = 0.007 ))</td>
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<tr>
<td>IES&lt;sup&gt;14&lt;/sup&gt;</td>
<td>55.7</td>
<td>Exemestane</td>
<td>Sequential</td>
<td>Yes (HR, 0.76; ( P = 0.0001 )) ER/+ unknown (HR, 0.83; ( P = 0.05 ))</td>
<td>No</td>
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<tr>
<td>ARNO 95&lt;sup&gt;15&lt;/sup&gt;</td>
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<td>Anastrozole</td>
<td>Sequential</td>
<td>Yes (HR, 0.66; ( P = 0.049 )) Yes (HR, 0.53; ( P = 0.045 ))</td>
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<tr>
<td>ITA&lt;sup&gt;16,17&lt;/sup&gt;</td>
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<td>Anastrozole</td>
<td>Sequential</td>
<td>Yes (HR, 0.57; ( P = 0.005 ))</td>
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<tr>
<td>ABCSG 8/ARNO 95&lt;sup&gt;18&lt;/sup&gt;</td>
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<td>Anastrozole</td>
<td>Sequential</td>
<td>Yes (HR, 0.60; ( P = 0.0009 )) No</td>
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<td>MA-17&lt;sup&gt;19,20&lt;/sup&gt;</td>
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<td>Letrozole</td>
<td>Extended</td>
<td>Yes (HR, 0.58; ( P &lt; 0.001 )) Node-positive only (HR, 0.61; ( P = 0.04 ))</td>
<td>No</td>
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<tr>
<td>ABCSG 6a&lt;sup&gt;21&lt;/sup&gt;</td>
<td>62</td>
<td>Anastrozole</td>
<td>Extended</td>
<td>Yes (HR, 0.62; ( P = 0.031 )) No</td>
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<tr>
<td>NSABP B-33&lt;sup&gt;22&lt;/sup&gt;</td>
<td>30</td>
<td>Exemestane</td>
<td>Extended</td>
<td>No</td>
<td></td>
</tr>
</tbody>
</table>

ATAC = Anastrozole, Tamoxifen, Alone or in Combination; BIG = Breast International Group; IES = Intergroup Exemestane Study; ARNO = Arimidex-Nolvadex; ITA = Italian Tamoxifen Anastrozole; ABCSG = Austrian Breast and Colorectal Cancer Study Group; NSABP = National Surgical Adjuvant Breast and Bowel Project; HR = hazard ratio; ER+ = estrogen receptor-positive

*“Upfront” denotes initial treatment with tamoxifen or an aromatase inhibitor; “sequential” denotes use of an aromatase inhibitor after 2–3 years of tamoxifen therapy; “extended” denotes use of an aromatase inhibitor after the completion of 5 years of tamoxifen therapy.
Initial Therapy: ATAC

Disease-Free Survival: Curves Shown for HR+ Patients; Median Follow-Up 68 Months

<table>
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<tr>
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<th>HR</th>
<th>95% CI</th>
<th>P-Value</th>
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<tbody>
<tr>
<td>HR+</td>
<td>0.83</td>
<td>(0.73-0.94)</td>
<td>0.005</td>
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<tr>
<td>ITT</td>
<td>0.87</td>
<td>(0.78-0.97)</td>
<td>0.01</td>
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Efficacy Summary

- Disease-free survival
- Time to recurrence
- Contralateral breast cancer
- Time to distant recurrence
- Overall survival
- Time to breast cancer death

* Odds ratio computed instead of hazard ratio

Hazard ratio (A, T) and 95% CI
BIG-198

5 years upfront letrozole vs 5 years tamoxifen.

Similar benefit to previous studies in favour of AI.

Patients were allowed to crossover from Tamoxifen arm and receive an AI after interim results showed a benefit.

This probably diluted the results & the ‘actual’ benefit of letrozole is likely to be higher.
Recruitment
4724 post-menopausal women from 37 countries were randomized between 1998 and 2003.

Results
The results were published in the New England Journal of Medicine in March 2004 on the recommendation of the Independent Data Monitoring Committee.
This early release of results was prompted by a highly significant early disease free survival benefit, which exceeded the predefined statistical stopping boundary.
An updated analysis in 2007 reported continued disease free survival benefit and a modest but real benefit in terms of overall survival.
The situation 2004-2009

On the basis of the results of these trials it was recommended that higher risk (node positive) ER+ve post-manopausal women were treated with 5 years of upfront aromatase inhibitor.

All but low risk women followed a switch policy with 2-3 years tamoxifen followed by 2-3 years of an AI.

Very low risk women were treated with 5 years of Tamoxifen with little/no benefit of adding in an AI.
BIG-198-A very important trial!

When initial results of other upfront/switching trials became available the BIG 198 study was expanded.

What started as a direct 5yr upfront comparison of Tamoxifen vs Letrozole was expanded to include 2 crossover arms.

There had also been no comparisons of 5yr AI vs switch.

It was felt that sequential therapy may be superior especially if the AI was given first.
BIG 198 Results- Current Guidelines

5 years upfront Letrozole is superior to Tam-Letrozole switch in node positive disease.

Sequential treatment Letrozole-Tam is identical to 5yrs letrozole. No benefit to switching.

On the basis of this NICE (March2009) recommendations are for 5yrs upfront AI (either anastrazole or letrozole) in all but low risk women.

We no longer commence women on a switch policy.
However some node-negative women will still be on tamoxifen as part of a switching plan and should be switched to an AI after 2 years.

Pre/perimenopausal women will continue on 5yrs Tamoxifen even if they appear to have become post menopausal during treatment.
Extended Adjuvant Therapy

Although increasingly rare there may still be a subgroup of women who have completed 5yrs of Tamoxifen and not had an AI

The MA.17 trial assessed letrozole therapy after 5 years of tamoxifen treatment, finding patients with node-positive disease exhibited significantly improved disease-free and overall survival with extended use of letrozole.

When trial showed a significant reduction in recurrence patients on the placebo arm were allowed to swap to receive letrozole and a benefit was present in this group even though there was a gap of up to 2-3 years from finishing Tamoxifen
AI side-effects

- **Hot flushes:**
  - Usually settle after 3-6 months.

- **Arthralgia/Joint Stiffness:**
  - Simple analgesia as required.
  - Often settles over 2-3 months
  - Can consider alternate AI? Letrozole better

- **Bone demineralisation:**
  - Baseline DEXA
  - Adcal/D3
  - T-score <-2.0 add bisphosphonate ie actonel once weekly.
  - Repeat DEXA after 18 months if osteopenic on initial scan.
  - Do not need to repeat if normal.
Hormone Therapy-Summary

- 5yrs of Tamoxifen significantly decreases recurrence (11%) and improves overall survival (9%) in ER+ breast cancer in pre and post menopausal women.
- Aromatase inhibitors provide an additional DFS benefit (3-4%) and 5 years upfront therapy should be considered in all but low risk women.
- AI’s do not work in pre-menopausal women.
- Women on a switch policy should continue to switch at 2yrs as planned.
- Extended therapy (with letrozole for 3-4years) should be considered in non-low risk women who have missed out on an AI. There is evidence for a benefit even if it is not started immediately.
What is Radiotherapy?

- Radiotherapy is the treatment of disease by exposure to radiation.

- The radiation can be man made X-rays or from naturally occurring isotopes such as radium, cobalt, caesium, iridium.

- It can be delivered either as ‘external beam’ radiotherapy from outside the body or from within the body as internal radiotherapy ‘brachytherapy’

- Radiotherapy works by destroying the cancer cells in the treated area. Normal cells are also be damaged but they can usually repair.
Modern radiotherapy machines

- The Curies discovery of radium began a new era in medical treatment and research.

- Radium was used in various forms until the mid-1900s when cobalt and caesium units came into use. These were safer and are still widely used in developing countries.

- Modern linear accelerators have been developed since the late 1940s.
Factors influencing the effect of radiotherapy

- Total dose
- Dose per fraction
- Time interval over which dose is received
- Volume of tissue exposed
- Type of cell (its radiosensitivity)
- The type and energy of radiation delivered
Biologically Effective Dose

- Biological effective dose is dependent on total dose, dose per fraction and tissue sensitivity to radiation.

- 30Gy/15#, 20Gy/5# & 10Gy/1# are all biologically equivalent (BED = 60) in terms of tumour cell kill.

- Large fraction sizes cause more normal tissue damage (late effects) and are generally reserved for palliation.
Breast Cancer Doses

• Historically 50Gy/25# has been proven to significantly reduce recurrence & improve survival post WLE

• START trial 40/15# of 2.67Gy daily over 3 weeks is equivalent.

• FAST trial 28.5Gy/5# of 5.7Gy weekly over 5 weeks.

• Late effects: cosmesis/nerve damage
Tumour Bed Boost

- EORTC study showed a benefit of tumour bed boost in all women under 50yrs.

- High risk boost dose 16Gy/8# (age<40yrs, margins<1mm)

- Others 40-50yrs 10Gy/5#

- Most women over 50yrs with clear margins >2mm should not receive a boost
Aims of Radiotherapy

• To deliver a known, uniform dose of radiation to a well defined target volume whilst sparing the surrounding tissue.

• 3-D conformal CT planning accurately captures patient anatomy, allowing not only precise target definition but also exact dose calculation.
CT Planning
Breast Plans

Wedges can be used to absorb dose and compensate for different amounts of tissue.
Beam angles can be adjusted to avoid critical structures i.e., heart.
Forward planned IMRT

- Blue/Red represents the ideal dose.
- Fig B uses more fields to even out ‘hotspots’
Partial Breast Irradiation

- As RT techniques have improved and we are able to accurately deliver doses to a specific area. The principal of whole breast irradiation is being questioned.

- Studies of partial breast irradiation are promising.

- PBI requires accurate tumour localisation and clips to the tumour bed are now routine.

- We utilise these to define the boost target volume
Respiratory gating technique.

Breath-hold respiratory gating is a recent technological advancement used to minimize radiation dose to the heart when treating left-sided breast cancers.

This technique takes advantage of the fact that when a person takes in a deep breath, the heart can move down and out of the path of the radiotherapy beam.

The patient has a small marker placed on her upper abdomen that can be detected by an infrared camera system to track the patient’s breathing cycle.

The patient is then asked to take a deep breath and hold. The radiation beam will automatically turn off when the patient’s breathing falls out of the desired range.
Varian's New RapidArc® Radiotherapy Technology

• A single arc can deliver essentially similar dose distributions compared with IMRT plans that incorporate as many as 36 fields.
• The most complex plans are delivered in <2mins compared with IMRT which takes 1min/field (typically 15mins)
Any Questions?