Radiation Therapy and Hormone Therapy in Breast Cancer

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Overview

- Review Breast Cancer and Staging
- Role of Radiation Therapy (RT)
- Radiation Therapy Process
- Side Effects RT
- Chemotherapy – Timing RT and Trastuzumab
- Hormone Therapy
- Summary
Breast Cancer – Incidence and Age

- Most common cancer in Maori and Non-Maori women – 65.1 vs 53.9 per 100,000 respectively*
  - Mortality to incidence 33% vs 24%*
  - Second among deaths from cancer (behind lung)

- Age: increases with age – one in eleven women
  - 0.43% women develop breast cancer < age 40yrs
  - 4% women between ages 40 and 59
  - 6.88% women between 60 and 79
  - Incidence declines after 80 years old

Breast Cancer – Risk Factors

- 99 Female to 1 Male
- Childbearing and Breastfeeding protective
  - Age < 25yrs at first birth = 50% reduction c/w nulliparous
- Early Menarche and Late Menopause increased risk
  - Exogenous Oestrogen
- Increased Body Mass Index
  - Physical Activity, Dietary
  - Alcohol
- Geographical
  - 5 USA : 1 Japan

- Family History
  - 2° relative 1.5x RR
  - 1° relative 1.7 to 2.5 RR
  - Risk increases with number of relatives diagnosed
  - BRCA1/BRCA2 mutations
  - p53 mutations
- Personal History Neoplasm
  - 10 to 15% risk contralateral breast cancer with previous
  - DCIS/LCIS
  - ADH, fibroadenoma
- Previous RT exposure – Mantle RT

RR = relative risk
Pathology Breast Cancer

- Ductal Carcinoma  70-80%
  - Rock hard, graded 1 - 3
- Lobular Carcinoma  5-10%
  - Can be multifocal and mammographically occult
  - MRI both breasts
- Medullary Carcinoma  1-5%
  - 13% BRAC1 therefore occurs in younger women
- Mucinous Carcinoma  1-3%
  - Occurs in older woman, slow growing, good prognosis
- Tubular Carcinoma  2%
  - Usually small, can be multifocal and bilateral, excellent prognosis

- **T = Tumour**
  - T1 < 2cm
    - T1a, T1b, T1c
  - T2 2 to 5cms
  - T3 > 5cms
  - T4
    - T4a extension to chest wall
    - T4b involvement skin
    - T4c both T4a and T4b
    - T4d inflammatory

- **N = Nodal**
  - Pathological and Clinical
    - N1 mobile ipsi axilla
    - N2 matted ipsi axilla
      - N2a and N2b
    - N3 ipsilateral supraclavicular
      - N3a, N3b, N3c

- **M = Distant Metastases**
### Stage Grouping Breast Cancer

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<th>Tumor Size (T)</th>
<th>Node Size (N)</th>
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<td>IV</td>
<td>T4</td>
<td>N0-2</td>
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M1 = Metastasis in lymph nodes
Prognostic variables in breast ca.

- **Major (histological):**
  - Histological variant
  - Tumour size
  - Tumour grade
  - Nodal status
  - Hormone receptor status
  - Distant metastases

- **Others including clinical trials:**
  - Proliferation markers – Ki-67, mitotic index…
  - Oncogenes, angiogenesis
  - Lymphovascular invasion
  - Age at diagnosis
  - Palpability of primary or nodal metastases
Surgery for Breast Cancer

- **Basis of management**
- **Breast Conservation**
  - Aim to maximise local control with good breast cosmesis
  - Wide local excision (negative margins)
  - Quadrantectomy
- **Mastectomy**
- **Axillary Surgery**
  - Sentinel node biopsy
  - Axillary Dissection
Contraindications to Breast Conservation

- Individual choice
  - After full discussion treatment options
- Tumour size
  - Too large to give good cosmetic outcome
- Margins
  - Clear margins not possible
  - Multifocal disease
- Previous Radiation Therapy/ Radiosensitivity
Radiation Therapy for Breast Cancer

Role
Dose Fractionation
Process Radiation Therapy
Toxicity
Role of Radiation Therapy

- Ductal Carcinoma In Situ (DCIS)
- Breast Conservation
- Post-Mastectomy
- Loco-regional – post-operative
- Definitive
  - Locally advanced and surgery not possible
  - Inflammatory
  - Patient factors (request)
DCIS

- Wide local excision (no nodal dissection)
  - Risk of subsequent DCIS/Malignant tumour ~1% per year
- Randomised Controlled Trials all show reduction in subsequent breast recurrence, however not all patients require adjuvant RT
  - Grade 2/3, any necrosis, margin 1mm
  - Avoid grade 1, unicentric, and
    - less than 1cm tumour with margin >1cm

- TROG 07.01 Adjuvant RT in DCIS
TROG 07.01 Adj RT in DCIS trial

- Assesses role of boost and different standard whole breast dose fractionation schedules

- Four arms:
  - 42.5Gy in 16 fractions (wb) whole breast (WB)
  - 42.5Gy in 16 # WB plus boost – 16Gy in 8#
  - 50Gy in 25 fractions WB
  - 50Gy in 25 # plus boost

- Entry criteria
  - Age < 50 yrs
  - Age > 50 yrs, plus one other risk factor
  - Tumour size > 15mm
  - Int/high grade, multifocal
  - Tumour necrosis…
Early Breast Cancer Radiation Therapy

- **Indications:**
  - Wide local excision with negative margins
  - Post-Mastectomy
    - T3 (over 5cm primary)
    - Positive margin
    - Heavy nodal involvement (>3 nodes)
    - Node negative and other risk factor
      - Grade 3
      - Lymphovascular invasion
Evidence for Breast Irradiation

- Four Randomised Controlled Trials (RCTs) of lumpectomy with or without breast irradiation
  - NSABP B06 50Gy/25#
  - Uppsala-Orebro BCSG 54Gy/27#
  - Milan 50Gy + 10Gy
  - Ontario clinical oncology group 40Gy/16# + 12.5Gy boost
NSABP B06

- 2105 women
- Modified radical mastectomy
- Lumpectomy + RT
- Lumpectomy

Recurrence rate
10%
35%
p<0.001

- No difference in overall survival
Meta-analysis Breast Conserving Surgery and Adjuvant RT

- Early breast cancer trialists’ collaborative group
  - 45 trials - Surgery + RT vs no RT
  - 19582 women, individual patient data
- Decrease local recurrence by 2/3rds
- Small decrease in breast cancer mortality, but increased non-breast cancer mortality
Timing Adjuvant RT

- No RCTs
- Conflicting evidence
- Data from 4 RCTs comparing WLE +/- RT started RT within 6 to 12 weeks
  - Two large cohort studies inconclusive

=> max interval surgery to RT 12 weeks
Timing chemotherapy (CT) and RT

- Optimal sequence unknown
  - CT then RT, eg CAF
  - CT and synchronous RT, eg CMF
  - RT then CT
  - CT, sandwich RT, then CT

- Five cohort studies assessing sequencing chemotherapy and RT
  ➔ CAF then RT reasonable
Dose Fractionation Adjuvant RT

- Four RCTs
  - 45Gy/ 25# vs 23Gy/ 6# (two weeks)
  - 50Gy/ 25# vs 42.9Gy/ 13# vs 39Gy/ 13#
  - 50Gy/ 25# vs 40Gy/ 15#
  - 50Gy/ 25# vs 42.5Gy/ 16#

- 42.5Gy in 16 fractions or 50Gy in 25 fractions
To Boost or Not to Boost?

- **EORTC ‘boost vs no boost’ trial**
  - 5569 women
  - 50Gy in 25 fractions
  - 16Gy in 8 fraction boost

- **Recurrence rate 50Gy / 25# + Boost**
  - Overall 7.3% 4.3% (p<0.001)

- Women less than 50yrs benefited most

- Poorer cosmesis in boost group

# Bartelink et al NEJM 2001; 345:1378-87
Adjuvant Supraclavicular RT

- Indications
  - More than 3 positive axillary nodes
  - Postmastectomy irradiation, except when positive tumour margins
  - 50Gy in 25 fractions (37.5Gy in 15 fractions)
Adjuvant Axilla Radiation Therapy

- **RT alone:**
  - Clinically negative axillary nodes and
  - Elderly or medically unfit patients
  - Women who wish to avoid axillary surgery

- **RT post axillary dissection**
  - Pathological evidence residual disease
  - 10 or more positive axillary nodes
  - 70% or more harvested nodes involved
  - Less than formal axillary dissection and positive nodes
Internal Mammary Chain Adjuvant RT

- Controversial in early stage disease
  - TROG participating in MA20 trial

- Problems:
  - Isolated IMC relapse rare
  - Unproven benefit
  - Anatomical location varies between patients
  - Potentially severe late cardiac/respiratory toxicity

- Consider in biopsy proven sentinel node
Post-Mastectomy RT

- Many unanswered questions
- Meta-analysis of RCTs\(^1\)
  - Reduction in local recurrence by two thirds
  - Reduction breast cancer specific mortality 6%
  - Increase in mortality from other causes
  - No overall survival benefit
- Two RCTs\(^2,3\) show 9-10% survival benefit

2. 3. Overgaard NEJM 1997;337:949-955
Indications for Post-Mastectomy RT

- Primary greater than 5cm
- Positive margins
- More than 3 positive axillary nodes
- Smaller tumours or 1 to 3 positive axillary nodes and
  - lymphovascular invasion, and/or
  - grade 3 disease
- Proposed TROG trial assessing role in T2 disease
Definitive Radiation Therapy

- **Locally Advanced Breast Cancer**
  - Usually have neoadjuvant chemotherapy +/- Trastuzumab
  - Hormone receptor positive – neoadjuvant Hormone Therapy
  - If operable – resection then post-operative RT
  - If not operable – locoregional RT will improve control
    - 50Gy in 25 fractions to Breast, SCF and Axilla
    - 10Gy in 5 fraction boost to residual

- **Inflammatory Breast Cancer**
  - Surgery increasing role post neoadjuvant therapy
Radiation Therapy Process

- **CT simulation**
  - “Breast Board”
  - CT scan
  - Permanent Dots (small Tattoos)

- **Dosimetry**
  - CT data sent to Dosimetry computers
  - Calculate dose distribution = “Planning”
High dose areas
New Machines @ CRCBS
Complications Breast Radiation Therapy

- **Acute = during RT**
  - Fatigue
  - Skin erythema/ moist desquamation
  - Breast pain
  - Swelling breast (oedema)

- **Late = Permanent**
  - Permanent Dot
  - Skin – pigmentation/ fibrosis/sun sensitivity
  - Breast Texture
  - Costochondritis/rib #
  - RT pulmonary fibrosis
  - Cardiac
  - Second Malignancy
  - Lymphoedema
  - Nerve Damage
Hormone Therapy in Breast Cancer

Roles
Tamoxifen
Aromatase Inhibitors
Hormone Therapy in Breast Cancer

- Roles
  - Adjuvant
    - Post surgery, chemotherapy, RT
    - With Herceptin
  - Neoadjuvant
    - Before surgery/RT
  - Palliative

All tumours are tested for Oestrogen Receptor (ER), Progesterone Receptor (PR) status
- Oestrogen receptor status: Positive (Allred/Quick score 8/8; 100% nuclei with strong staining)
- Progesterone receptor status: Positive (Allred/Quick score 7/8; 5% nuclei with moderate staining)
- HER2 IHC: Equivocal (2+). Tissue has been forwarded to IGENZ in Auckland for FISH
  - (FISH testing shows no amplification of HER-2)
Adjuvant! Online
Decision making tools for health care professionals

Adjuvant! for Breast Cancer (Version 8.0)

Patient Information

Age: 60
Comorbidity: Perfect Health
ER Status: Positive
Tumor Grade: Grade 3
Tumor Size: 2.1 - 3.0 cm
Positive Nodes: 1 - 3
Calculate For: Mortality
10 Year Risk: 45 Prognostic

Adjuvant Therapy Effectiveness

Horm: Tamoxifen (Overview 2000)
Chemo: CA*4 then T*4

No additional therapy:
- 51.7 alive in 10 years.
- 44.0 die of cancer.
- 4.3 die of other causes.

With hormonal therapy: Benefit = 11.1 alive.
With chemotherapy: Benefit = 8.9 alive.
With combined therapy: Benefit = 18.3 alive.

Print Results PDF | Access Help and Clinical Evidence

Images for Consultations

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Tamoxifen

- Nonsteroidal Oestrogen Antagonist in Breast Tissue
  - Competitive binder on Oestrogen receptor
    - Causes cells to remain in $G_0$ and $G_1$ stages of cell cycle
    - Cytostatic, not cytocidal
  - Other tissues behaves as agonist
    - Endometrium, Bones, Heart
- Useful in pre- and post-menopausal women
  - Male breast cancer
- Found in 1950s
- First clinical trial 1970s
- Recognised in conjunction with chemotherapy to improve survival 1980 trial
  - Widely used since
- Initially given for two years
  - five years
- Investigated for ten years adjuvant treatment
  - ATLAS study
Tamoxifen Side Effects

- **Adverse**
  - HOT FLUSHES
  - GI intolerance
  - Risk DVT doubled
  - Suppression mensturation
  - Vaginal bleeding/discharge
    - Risk Endometrial cancer – 2 to 4x normal population
  - Alopecia
  - Weight gain/fluid retention
  - Rare retinopathy/cataracts

- **Beneficial**
  - Bone – inhibits osteoclasts, therefore prevents osteoporosis
  - Lipid profile improves
Aromatase Inhibitors (AIs)

- Inhibit Aromatase enzyme
  - Converts androgens into oestrogen
- Main source of Oestrogen in premenopausal women is the ovaries
- In post-menopausal women most of Oestrogen is produced via the conversion of androgens into Oestrogen by the aromatase enzyme in the peripheral tissues, eg adipose tissue and a number of sites in the brain

Three AIs

- Anastrazole (Arimidex)
  - Nonsteroidal AI
  - 1mg daily
- Letrozole (Femara)
  - Nonsteroidal AI
  - 2.5mg daily
- Exemestane (Aromasin)
  - Steroidal AI, non-reversible
  - 25mg once daily

- Only work in post-menopausal (or premenopausal with ovarian suppression)
Aromatase Actions

Aromatase converts Testosterone to Oestodiol

Aromatase converts Androstenedione to Oestone
Side Effects Aromatase Inhibitors

- **Very common**
  - Hot Flushes, vaginal dryness
  - GI upset
  - Fatigue
  - Musculoskeletal pain
  - Headache

- **Common**
  - Depression
  - Alopecia
  - Weight gain

- **Bone demineralisation**
  - Not protective like Tamoxifen
  - Bone lost at same or faster rate as post-menopausal women
  - Bone density scan
  - Cholecalciferol (Vit D) 1.25mg monthly
  - Aledronate (Fosamax) 70mg weekly (Fosamax plus with Vit D)
    - Must remain upright over 30mins
A Randomized Trial of Letrozole in Postmenopausal Women after Five Years of Tamoxifen Therapy for Early-Stage Breast Cancer

Paul E. Goss, M.D., Ph.D., James N. Ingle, M.D., Silvana Martino, D.O., Nicholas J. Robert, M.D., Hyman B. Muss, M.D., Martine J. Piccart, M.D., Ph.D., Monica Castiglione, M.D., Dongsheng Tu, Ph.D., Lois E. Shepherd, M.D., Kathleen I. Pritchard, M.D., Robert B. Livingston, M.D., Nancy E. Davidson, M.D., Larry Norton, M.D., Edith A. Perez, M.D., Jeffrey S. Abrams, M.D., Patrick Therasse, M.D., Michael J. Palmer, M.Sc., and Joseph L. Pater, M.D.

Abstract

Background
In hormone-dependent breast cancer, five years of postoperative tamoxifen—but not tamoxifen therapy of longer duration—prolongs disease-free and overall survival. The aromatase inhibitor letrozole, by suppressing estrogen production, might improve the outcome after the discontinuation of tamoxifen therapy.

Methods
We conducted a double-blind, placebo-controlled trial to test the effectiveness of five years of letrozole therapy in postmenopausal women with breast cancer who have completed five years of tamoxifen therapy. The primary end point was disease-free survival.

Results
A total of 5187 women were enrolled (median follow-up, 2.4 years). At the first interim analysis, there were 207 local or metastatic recurrences of breast cancer or new primary cancers in the contralateral breast—75 in the letrozole group and 132 in the placebo group—with estimated four-year disease-free survival rates of 93 percent and 87 percent, respectively, in the two groups (P≤0.001 for the comparison of disease-free survival). A total of 42 women in the placebo group and 31 women in the letrozole group died (P=0.25 for the comparison of overall survival). Low-grade hot flashes, arthritis, arthralgia, and myalgia were more frequent in the letrozole group, but vaginal bleeding was less frequent. There were new diagnoses of osteoporosis in 5.8 percent of the women in the letrozole group and 4.5 percent of the women in the placebo group (P=0.07); the rates of fracture were similar. After the first interim analysis, the independent data and safety monitoring committee recommended unblinding and prompt communication of the results to the participants.

Conclusions
As compared with placebo, letrozole therapy after the completion of standard tamoxifen treatment significantly improves disease-free survival.
Adjuvant! for Breast Cancer (After 5 Years of Tamoxifen)

Patient Information

Present Age: 60
Comorbidity: Perfect Health
ER Status: Initially Positive
Tumor Grade: Grade 3
Tumor Size: 2.1 - 3.0 cm
Positive Nodes: 1 - 3
Initial 10 Year Risk: 68 Prognostic

Projections over the next 5 years
(after 5 years of Tamoxifen)

No additional therapy after 5 years of Tamoxifen:

- 72.1 alive and without relapse in 5 years.
- 26.4 relapse (local, regional or distant)
- 1.5 die of other causes.

Letrozole following 5 years of Tamoxifen:

- 72.1 alive and without relapse. Plus...
- 9.7 alive and without relapse due to letrozole.
- 16.7 relapse.
- 1.5 die of other causes.

Initial Adjuvant Therapy:
Patient must have received 5 years of Tamoxifen.
Initial chemotherapy does not affect late events.
LHRH Analogues

- Goserelin (Zoladex)
  10.8mg three monthly
- Leuprolrelin (Lucrin)

Side Effects
- Hot flashes (pre-menopausal)
- Arthralgia
- Reduced bone density
- Loss libido, vaginal dryness
- Mood changes
- Headache
- **Flare** – symptomatic metastatic disease
Megestrol Acetate (Megace)

- Progesterone
  - Palliative management breast and endometrial cancer

- Adverse effects
  - Weight gain, DVT, GI upset, Headache, Oedema
  - Vaginal bleeding
  - Heart failure and hypertension
  - Hot flushes, mood changes...
Summary

- Breast Cancer Overview
- Radiation Therapy
  - Adjuvant
  - Loco-regional
  - Definitive
- Simulation Process
- Toxicity

- Hormone Therapy
  - Tamoxifen
  - Aromatase Inhibitors
  - LHRH analogues

- Roles
  - Adjuvant
  - Palliative
  - Extended Adjuvant