Quality of Life of women undergoing mastectomy with Immediate, Delayed or No breast reconstruction and adjuvant radiotherapy for breast cancer (QoLID): A pilot study to assess feasibility

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Background

- BC most common malignancy in women
- 30-50% will undergo mastectomy\(^1\)
- ~50% would choose BR if offered it\(^2\)
- Clinical guidelines recommend breast reconstruction (BR) to all suitable women requiring or choosing mastectomy (NCI, NCCN, NICE, Cancer Australia).

- BR rate 6-16% (ANZ)\(^3\)
  - Regional & centre differences
    - 41% Sydney metropolitan centre\(^4\)
    - 28% NZ\(^5\)
  - International differences (Range 5-82%)\(^2\)
    - 25% USA
    - 21% UK
Factors of Reconstruction

**Associations**

- **Patient/tumour factors**
  - young age, caucasian ethnicity, private health insurance, higher level of education/income, early stage tumour, insitu disease, less adjuvant therapy

- **Surgeon/hospital factors**
  - geographic variation; urban location, teaching hospital, high volume breast unit, on site plastic surgery unit

- **Psychological/other factors including patient’s choice**

**Barriers**

- **Co-morbidities**
  - high BMI, diabetes, IHD, old age

- **Smoking**

- **Adjuvant Radiotherapy & Chemotherapy**
  - Interference w delivery of radiation with implant in situ
  - Concerns about PMRT impacting on quality of BR
  - Anxiety around possible delay in starting adjuvant systemic therapy due to complications from BR surgery
SURGEON
“I don’t think so”

MED ONC
“I agree it may delay chemo”

RAD ONC
“I agree it makes RT harder”
What do we know

Traditional approach for patients needing PMRT is delay BR (DBR).
  - 2 yr waiting period after mastectomy\textsuperscript{9}
  - Many don’t undergo reconstruction at all\textsuperscript{10}
    - Choice
    - Lack of access to public health facilities
    - 2-5 years wait in NZ\textsuperscript{4}
Safety

- Meta-analysis\textsuperscript{11} of 10 studies showed no evidence for increased frequency of local or systemic cancer recurrence with immediate BR (IBR) compared with mastectomy alone.

- Studies\textsuperscript{12,13} show feasibility of IBR (implant or autologous) in women requiring adjuvant systemic therapy and PMRT

  - Not impairing ability to detect local recurrence\textsuperscript{14}
  - Not causing significant delays in adjuvant therapy\textsuperscript{15}
  - Acceptable rates of complications
  - High levels of patient satisfaction

Limitations

- Retrospective, lead time bias, tools used does not fully assess the surgical outcomes of BR, not looked at patients having adjuvant treatments, only looks at one type of BR, not all groups compared etc...
Benefits of BR

› Reduce anxiety
› Improve psychological well-being
› Improve ability to cope with negative emotional and psychological consequences of mastectomy
› Majority are satisfied with their BR
› Enhance quality of life
› No detrimental effect on loco-regional control or survival
If IBR improves QoL of patients undergoing PMRT and adjuvant treatments, then should IBR be offered to all breast cancer patients who are reasonable candidates for this procedure and not deprive patients of the ability to choose?
How do breast cancer treatments affect a patient?

Proximal Effects

Surgery
- Early complications
  - Implant infection
  - Flap/implant failure
  - Acute bleeding, haematoma
- Late complications
  - Capsular contraction
  - Poor symmetry
Aesthetic
- Symmetry, shape, volume, size, texture
Surgery-related symptoms
- Pain/discomfort
- Swelling
- Stiffness/tightness (beast, chest, axilla, shoulder, arm)

Chemo- & Radio-therapy
- related side-effects and complications

Psychological
- fear, anger, uncertainty, anxiety, depression

Functioning & well-being
- Physical
- Emotional
- Social
- Role
- Cognitive
- Body image
- Sexual function

Process of care
- Satisfaction with health care/providers/information
- Preferences / regret
- Inconvenience

Global QOL, Well Being & Happiness

Other aspects of life
- Finances, family, job, safety, security

Compliments of Professor Madeleine King
QoLID Pilot Study Design

- Prospective cohort observational study
  - Multi-centre
    - results of one centre analysed here
  - Serial surveys at various intervals
  - Aim minimum 20 patients in each arm
    - Yield a point estimate for the difference between groups on a given continuous outcome parameter with a 95% confidence interval that extends no more than +/- 0.7 of a standard deviation (with 80% probability). This level of precision is considered sufficient to yield adequate estimates of the plausible effect size to inform the design of any subsequent definitive cohort study.
  - Duration - At least 2 years
Why this study?

• 1st prospective study assessing women with ‘higher risk breast cancer’ requiring mastectomy +/- BR and PMRT, in Australia & New Zealand.

• Better understanding of:
  1. Patients undergoing BR and timing of BR.
  2. Choice between women choosing BR vs Mx.
  3. Barriers to BR
     - Complications
     - Aesthetic outcomes
     - Safety of offering BR to these ‘higher risk’ patients

• Identify and provide adequate long-term social support for patients choosing BR (IBR or DBR) or mastectomy alone.
Women with breast cancer requiring mastectomy + PMRT +/- breast reconstruction

1. Mastectomy
   - Immediate breast reconstruction (IBR)
     - Implant
     - 1-stage
     - 2-stage
     - Autologous (few)
       - LD
       - TRAM/DIEP
     +/- Adj Chemo/PMRT

2. Mastectomy +/- Adj Chemo/PMRT

3. Mastectomy (NBR)
   +/- Adj Chemo/PMRT

Delay breast reconstruction (DBR)
- Autologous
  - LD
  - TRAM/DIEP
To determine;

- the feasibility of prospective recruitment
- assessment of PROs describing a comprehensive range of QoL measures in IBR, DBR, NBR women following mastectomy and PMRT for breast cancer.

Lessons learned will inform the design of a definitive multi-site study of these outcomes.
Objectives

The primary objective is..

- To determine the feasibility;
  - Assessing a comprehensive range of PROs in women choosing IBR, DBR or NBR, and requiring PMRT
  - Assessing completion rates of PRO questionnaires up to a week before surgery, 1 month, 3 months, 12 months, 18 months, 24 months, then annually until 5 years.
The secondary objectives are to obtain preliminary estimates of the following endpoints to inform sample size calculation of the definitive study:

1. Rate of patient acceptability of IBR (prior to breast cancer surgery)
2. Patient-assessed aesthetic outcomes (compared with patient assessment at baseline) at 1 month, 3 months, 12 months, 18 months and 24 months, and then annually for up to 5 years
3. Surgeon-assessed aesthetic outcomes (compared with surgeon assessment at baseline) at 12 and 24 months
4. Rate and type of surgical complications
5. Measures of pain as experienced by patients undergoing IBR, DBR or NBR
6. Overall rate, and cause-specific rates, of delays in delivery of adjuvant treatments (chemotherapy, radiotherapy, endocrine therapy and targeted therapy).
1. Patients undergoing mastectomy and PMRT will be willing to participate in a cohort study involving a series of PRO assessments over 5 years after diagnosis of early stage breast cancer.

2. PRO completion rates will be high (≥90% in the first year of study participation, ≥80% in the second year).

3. IBR will provide better PROs across a range of issues compared to DBR and NBR women undergoing mastectomy and PMRT.

4. IBR (implant or autologous) does not significantly delay the delivery of adjuvant therapies for breast cancer patients.
1. Quality of Life

2. Body Image\textsuperscript{18,19}
   - Positive association w BR
   - Better body image with BR than mastectomy

3. Pain\textsuperscript{20,21}
   - Acute to chronic states
   - Post mastectomy pain syndrome (20-68%)
   - Pain post BR also documented
   - Difference in trajectory of pain syndromes between types of BR not documented
Patient Reported Outcome Measures (PROMs)

1. Quality of life

- EORTC QLQ C30 (30-item)
  - 15 sub-scales: physical function, role function, social & emotional function, cognitive function, pain, fatigue, nausea/vomiting, dyspnoea, lack of appetite, insomnia, diarrhoea, constipation, financial difficulties, global health/quality of life

- EORTC QLQ BR23 (23-item)
  - 8 sub-scales: breast symptoms, arms symptoms, body image, sexual functioning, sexual enjoyment, future perspective, systemic therapy side effects, upset by hair loss
- **Mastectomy module**
  
  Pre/post-op: *Satisfaction with breast, psychosocial well-being, physical well-being, sexual well-being*

  Additional for post-op: Satisfaction with plastic surgeon, satisfaction with medical team, satisfaction with office staff

- **Reconstruction module**

  Pre/post-op: *Satisfaction with breast, psychosocial well-being, physical well-being, physical well-being (abdomen), sexual well-being*

  Additional for post-op: *Satisfaction with breast (implant only)*
2. Body Image
   - Body Image after Breast Cancer Questionnaire (BIBC) (53 items)
     - 6 subscales: Vulnerability, Body Stigma, Capacity, General Body appearance, Transparency, Arm concerns

2. Pain
   - Brief Pain Inventory-Short Form (BPI-sf) (8-item)
     - Severity of pain and impact on daily functioning, mood, walking ability, normal work, relations with others, sleep, enjoyment of life on a 10-point scale
     - 2 subscales: Severity & interference

   - Pain Catastrophizing Scale (PCS) (13-item)
     - To measure pain catastrophizing on a 5-point scale
     - 3 subscales: Helplessness, Rumination, Magnification
Inclusion & Exclusion Criteria

**Inclusion**

1. Women diagnosed with invasive breast cancer requiring mastectomy and likelihood of requiring PMRT.
2. Women treated with neo-adjuvant chemotherapy for invasive breast cancer and will be having mastectomy and PMRT.
3. Able and willing to complete study questionnaires for the duration of study.
4. Able to provide written & informed consent to participate in study.

**Exclusion**

1. Prophylactic or risk-reducing surgery
2. Previous radiotherapy to the breast or chest precluding standard radiotherapy
3. Loco-regional recurrence precluding further radiotherapy
4. Previous wide local excision requiring completion mastectomy without the need for PMRT
5. Pregnant women
6. Distant metastatic disease
7. Inflammatory breast cancer
PMRT

› **Indications**\(^{22,23}\)
  - 4 or more positive axillary lymph nodes (N2)
  - Tumour size 5 cm or more (T3/T4)
  - Positive/very close margin for invasive disease where no further local surgery feasible.

› **Patients with 1 to 3 positive nodes**
  - AR in locoregional recurrence of 16.1% at 5 yrs & AR in breast cancer survival of 8.1% at 15 yrs (Meta-analysis by EBCTCG of 20 RCTs)\(^{24}\)

› **NCCN Guidelines**\(^{25}\)
  - T3/T4, N1/N2, Mo
  - T1-2, N0 <1mm margins – consider chest wall PMRT
  - T1-2, N0 >1mm margins – no PMRT

› **ACR PMRT Guideline**\(^{23}\)
  - T3N1, T4N1/N2 primary tumors as well as T1-2 disease with 4 or more positive LNs.
  - Controversy
    - Benefit in patients with T1-2 disease and with 1 to 3 positive LNs.
    - Patients with pT3N0 tumors (conflicting data regarding impact on survival).

› ASCO updating recommendations, ASTRO presented recommendations, not yet published.
If IBR improves QoL of patients undergoing PMRT and adjuvant treatments, then should IBR be offered to all breast cancer patients who are reasonable candidates for this procedure and not deprive patients of the ability to choose.

Choice?
The importance of choice: A prospective evaluation of factors affecting preference for immediate, delayed or no breast reconstruction in the context of mastectomy and post-mastectomy radiotherapy for breast cancer

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A/Prof Andrew Spillane
Dr Meagan Brennan
Dr April Wong
Dr Kylie Snook
Dr Cindy Mak
Importance of Choice

› Initial questionnaires adapted from Reaby (1998)

> Three questionnaires with separate sets statements (IBR, DBR, NBR)

> 7 Domains: **Feeling good, Feeling normal, Being practical, Influence of others, Expectations, Fear, Timing and Unnecessary.**

> Mean response rate – way of comparing the strength of different domains within and across groups (maximum score of 1).
Importance of Choice

› Reasons for Immediate Reconstruction (RFIR) – 18 statements
  • “I want to feel good about myself” [Feeling Good]
  • “I want to feel more balanced” [Feeling Normal]

› Reasons for Delayed Reconstruction (RFDR) – 31 statements
  • “I’m too young to be without a permanent breast” [Feeling Normal]
  • “I want to regain my feminity”, “I want to feel good about myself”, “BR is essential for my emotional well-being” [Feeling Good]

› Reasons for No Reconstruction (RFNR) – 20 statements
  • “I did not want more surgery” [Being Practical]
  • “I only want to get rid of the cancer/BR is not essential for my emotional or physical well-being” [Unnecessary]
QoLID Pilot Results

› July 2013 – October 2014

› Total = 43
  - IBR = 27
  - DBR = 7
  - NBR = 9

› Recruitment rate;
  - 43/75 (/Mx + PMRT) = \textbf{57.3}\% 
  - 43/187 (/total Mx) = 23.0\%

› PRO completion rate;
  - 43/43 = \textbf{100}\%
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<td>Triple negative (ER, PR, HER2 negative)</td>
<td>Yes No</td>
<td>3 26</td>
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<td>Wound infection</td>
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<td>Lymphoedema</td>
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</table>
HRQoL Outcomes
HRQoL Outcomes

QLQ C30 role function

Better Function (Better)

Worse Function (Worse)

Mean (+/- 1 Standard Error)

Study Time Point

Baseline

3month

IBR
DBR
NBR
HRQoL Outcomes

QLQ C30 cognitive function

Better Function (Better)

Worse Function (Worse)

Mean (+/- 1 Standard Error)

Study Time Point

Baseline

3month

IBR
DBR
NBR
HRQoL Outcomes

![Graph showing QLQ C30 emotional function outcomes](image)

- Better Function (Better)
- Worse Function (Worse)
- Study Time Point: Baseline vs. 3 months
- Mean ± 1 Standard Error
- Outcomes for IBR, DBR, and NBR
HRQoL Outcomes

QLQ C30 social function

Mean (+/- 1 Standard Error)

Better Function (Better)

Worse Function (Worse)

Study Time Point

IBR
DBR
NBR
HRQoL Outcomes

QLQ C30 fatigue

More Fatigue (Worse)

Less fatigue (Better)

Mean (+/- 1 Standard Error)

Study Time Point

Baseline

3month

IBR

DBR

NBR
HRQoL Outcomes

QLQ C30 overall QOL/Health

Higher QOL/Health (Better)

Lower QOL/Health (Worse)

Mean (+/- 1 Standard Error)

Baseline

3month

Study Time Point

IBR

DBR

NBR
BIBC vulnerability

More Vulnerability (Worse)

Less Vulnerability (Better)

Study Time Point

Mean (+/- 1 Standard Error)

Baseline 1month

IBR DBR NBR
Breast & Arm symptoms

![BR23 breast symptoms graph]

More symptoms (Worse)

Less symptoms (Better)

Mean (+/- 1 Standard Error)

Baseline

3month

Study Time Point

IBR

DBR

NBR
Breast & Arm symptoms

BR23 arm symptoms

More symptoms (Worse)

Less symptoms (Better)

Study Time Point

Mean (+/- 1 Standard Error)
Breast & Arm symptoms

Breast Q physical wellbeing (chest)

Mean (+/- 1 Standard Error)

Higher Wellbeing (Better)

Lower Wellbeing (Worse)

Study Time Point

IBR
DBR
NBR
Pain

BPI severity

More Pain (Worse)

Less Pain (Better)

Mean (+/- 1 Standard Error)

Study Time Point

IBR
DBR
NBR
Pain

BPI interference

More Interference (Worse)

Less Interference (Better)

Mean (± 1 Standard Error)

Study Time Point

IBR
DBR
NBR
BREAST Q Domains

› With Outcome
  - IBR 67.42 (SE 3.93)

› With Information
  - IBR 71.86 (SE 3.46)

› With Surgeon
  - IBR 88.10 (SE 3.23)
  - DBR 83.71 (SE 7.79)
  - NBR 84.11 (SE 7.12)

› With Medical Team
  - IBR 93.78 (SE 3.64)
  - DBR 98.71 (SE 1.29)
  - NBR 89.78 (SE 4.79)
Limitations/Learning points

› Small numbers
  - CI all overlaps
  - Unable to ascertain definite comparison for any difference in outcomes statistically at this stage
  - Potential confounding issues e.g. neoadjuvant chemotherapy, previous lumpectomy, baseline post-op scores, which may need adjustment for in the future

› Distinct populations
  - Based on reasons for reconstruction
  - Could be signal to account for results
Limitations/Learning points

› It’s NOT a RCT!

- Quest Trial B – QOL following mastectomy + BR + PMRT
- Failed recruitment (n = 8 / 36)
  - Phase 3 multicentre RCT (IBR vs DBR)
  - Group 1: Immediate autologous LD
  - Group 2: Staged – delayed autologous LD
    - Delay 6 months if PMRT
    - Delay 12 months if PMRT + Adj chemo
  - Commenced Apr 2010, closed Dec 2011

- Conclusions:
  - Patient preference was the predominant reason for declining trial entry.
Phase 2 of pilot study

2-centre site (Sydney, Waikato)

Recruitment update (Total n = 65) (July 13 – Jun 15)

- Sydney
  - Total 58/64 (6 withdrawn)
    - IBR: 37
    - DBR: 11
    - NBR: 10

- Waikato (Dec 14 – Jun 15)
  - Total 7/12 (5 withdrawn)
    - IBR: 3
    - DBR: 4
    - NBR: 0
# Updated Schedule

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<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>1-2 weeks</th>
<th>1 months</th>
<th>3 months</th>
<th>6 months</th>
<th>12 months</th>
<th>18 months</th>
<th>24 months</th>
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</table>
1. Recruitment & PRO completion rates are good.

2. For women with ‘higher risk breast cancer’, IBR is a possible approach, with no immediate harm seen in the IBR group.

3. Similar trends in HRQoL and other PROs across 3 groups
   - Very early results, data may not be fully representative
   - ? Trends at 12 months f/u period

4. Results of the IBR group are sufficient to support the continuation of the study and conducting a well-powered study!
Future Directions

1. Long term large prospective study
   - To assess long term outcomes

2. Practice changing
   - IBR is an acceptable approach
   - Offering women the option of IBR in the setting of mastectomy, PMRT and women who desires BR by *giving women the choice*

3. Decision aid
   - To assist women in deciding whether BR is something that they desire to pursue and the timing of BR
References

Special thank you

Patients
Mr Daniel Costa
Ms Annette Kifley
Dr. Kathy Flitcroft
Ms Rebecca Karantonis

Ms Heather Flay
Ms Jenni Scarlet
Ms Heather Flay
Ms Jenni Scarlet