Intra operative “Intrabeam” radiation for breast cancer

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Radiation Oncologist

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Disclaimer/Conflicts

I am a radiation oncology consultant at

- Christchurch Hospital,
- Canterbury Breast Care,
- St Georges Cancer Centre
- Intrabeam is provided via Focus Radiotherapy

I have no financial interests with Focus Radiotherapy or the above institutions
Overview

- Role of radiation in Breast Cancer
  - Whole breast and partial breast radiation

- Intrabeam radiation
  - Randomised Trial evidence – TARGIT study
  - Controversy

- Practicalities of Intra beam
  - What does the procedure look like
  - What does it mean for the patient

- Intrabeam in NZ and Christchurch
Move from “maximal tolerable” to “minimum effective”

Radical Mastectomy  →  Breast Conservation

Axillary Clearance  →  Sentinel Node Biopsy
**Whole Breast Radiation Therapy (WBRT)**

EBCTCG Lancet 2011 meta analysis

- After breast conserving surgery

- WBRT with external beam radiation
  - halves risk of local recurrence in breast
  - reduces breast cancer death by 1/6
    - For every 4 recurrences prevented at 10 year, 1 breast cancer death is avoided at 15 years

- Radiation delivered Monday – Friday for 3 weeks
  - Time commitment
  - Side effects
External beam radiation
How does radiation work?
Radiation causes double strand breaks in DNA

- Radiation **indirectly** damages DNA by producing free radicals
- Radiation **directly** damages DNA
- Cancer cells do not repair DNA damage which leads to cell death
Do we need to treat the whole breast?

- Patterns of failure studies
- Local Recurrence occurs at or near the site of the primary tumour in the majority of cases
- Concept of partial breast irradiation
Partial Breast Irradiation (PBI)

- Deliver PBI with various technique
  - External beam radiation – megavoltage photons
  - Brachytherapy – interstitial catheters/balloons
  - Intra operative
    - Kilovoltage xrays – “Intrabeam”
    - Electrons

- Is appropriate for SELECTED patients
  - Guidelines from international groups
    - ASTRO, ESTRO, Brachytherapy Society
  - NICE (UK) have approved it in certain NHS hospitals
Table 1  Comparison of patient groups in original and updated consensus statements

<table>
<thead>
<tr>
<th>Patient group</th>
<th>Risk factor</th>
<th>Original</th>
<th>Update</th>
</tr>
</thead>
<tbody>
<tr>
<td>Suitability</td>
<td>Age</td>
<td>≥60 y</td>
<td>≥50 y</td>
</tr>
<tr>
<td></td>
<td>Margins</td>
<td>Negative by at least 2 mm</td>
<td>No change</td>
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<tr>
<td></td>
<td>T stage</td>
<td>T1</td>
<td>Tis or T1</td>
</tr>
<tr>
<td></td>
<td>DCIS</td>
<td>Not allowed</td>
<td>If all of the below:</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>• Screen-detected</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>• Low to intermediate nuclear grade</td>
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<td></td>
<td></td>
<td></td>
<td>• Size ≤2.5 cm</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Resected with margins negative at ≥3 mm</td>
</tr>
<tr>
<td>Cautionary</td>
<td>Age</td>
<td>50-59 y</td>
<td>40-49 y if all other criteria for “suitable” are met</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>≥50 y if patient has at least 1 of the pathologic factors below and does not have any “unsuitable” factors</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Pathologic factors:</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Size 2.1-3.0 cm $^a$</td>
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<td></td>
<td></td>
<td></td>
<td>• T2</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>• Close margins (&lt;2 mm)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Limited/focal LVSI</td>
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<td></td>
<td></td>
<td></td>
<td>• ER(-)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Clinically unifocal with total size 2.1-3.0 cm $^b$</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Invasive lobular histology</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Pure DCIS ≤3 cm if criteria for “suitable” not fully met</td>
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<td></td>
<td></td>
<td></td>
<td>• EIC ≤3 cm</td>
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<tr>
<td></td>
<td>Margins</td>
<td>Close (&lt;2 mm)</td>
<td>No change</td>
</tr>
<tr>
<td></td>
<td>DCIS</td>
<td>≤3 cm</td>
<td>≤3 cm and does not meet criteria for “suitable”</td>
</tr>
</tbody>
</table>

Unsuitable

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Original</th>
<th>Update</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>&lt;50 years</td>
<td>&lt;40 y</td>
</tr>
<tr>
<td>Margins</td>
<td>Positive</td>
<td>40-49 y and do not meet the criteria for cautionary</td>
</tr>
<tr>
<td>DCIS</td>
<td>&gt;3 cm</td>
<td>No change</td>
</tr>
</tbody>
</table>

$^a$ The size of the invasive tumor component.

$^b$ Microscopic multifocality allowed, provided the lesion is clinically unifocal (a single discrete lesion by physical examination and ultrasonography/mammography) and the total lesion size (including foci of multifocality and intervening normal breast parenchyma) falls between 2.1 and 3.0 cm.
What is the evidence for Intrabeam?
Risk-adapted targeted intraoperative radiotherapy versus whole breast radiotherapy for breast cancer: 5-year results for local control and overall survival from the TARGIT-A randomised trial

Jayant S Vaidya, Frederik Wenz, Max Bulsara, Jeffrey S Tobias, David Joseph, Mohammed Keshtgar, Henrik L Flyger, Samuele Massarut, Michael Alvarado, Christobel Saunders, Wolfgang Eiermann, Marinos Metaxas, Elena Sperk, Marc Sütterlin, Douglas Brown, Laura Esserman, Mario Roncadin, Alistair Thompson, John A Dewar, Helle M R Holtveg, Steffi Pigorsch, Mary Falzon, Eleanor Harris, April Matthews, Chris Brew-Graves, Ingrid Potyka, Tammy Corica, Norman R Williams, Michael Baum, on behalf of the TARGIT trialists’ group*

The Lancet Journal, published Online November 11, 2013
TARGIT A Trial

TARGIT-A is currently the largest multicenter randomized clinical trial in the field of Partial Breast Irradiation.

- 3451 patients
- 11 countries
- 33 centers
Eligibility Criteria

- ≥ 45 years
- ≤ 3 cm
- Grade 1 or 2
- ER positive
- Clinically node negative
- Clear margins
- No Lymphovascular invasion (LVI)
TARGIT-A design – ‘Non inferiority’

Over 12 years, 1721 women received the study treatment (TARGIT), compared to a control group of 1730 women who received standard EBRT treatment.

3451 patients aged 45 years and older with invasive ductal carcinoma
Randomization 1:1

- TARGIT: 1721 Patients assigned
- EBRT: 1730 Patients assigned

Age > 45, Unifocal invasive duct carcinoma, MRI not required, size preferably < 3.5 cm
Pre and post pathology stratum

<table>
<thead>
<tr>
<th>Prepathology stratum</th>
<th>Postpathology stratum</th>
</tr>
</thead>
<tbody>
<tr>
<td>TARGIT concurrent with lumpectomy</td>
<td>TARGIT given subsequently by reopening the wound (median time between primary surgery and post-pathology TARGIT treatment was 37 days)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>EBRT Arm</th>
<th>TARGIT Arm</th>
<th>EBRT Arm</th>
<th>TARGIT Arm</th>
</tr>
</thead>
<tbody>
<tr>
<td>1158 patients</td>
<td>1140 patients</td>
<td>562 patients</td>
<td>581 patients</td>
</tr>
</tbody>
</table>

2298 patients randomized TARGIT Prepathology vs. EBRT
1153 patients randomized TARGIT Postpathology vs. EBRT
What is the risk-adapted approach?

So called onesize-fits-all whole-breast radiotherapy versus individualised risk-adapted therapy – in which a proportion of patients who received TARGIT were also given EBRT if they were shown to have adverse tumour factors. This situation was expected in 15% of cases and was incorporated into the power calculations.

**EBRT**
- Standard fractionated EBRT
  - in 15-25 fractions
  - +/- Boost

**TARGIT**
- TARGIT single dose (20 Gy) with INTRABEAM®
  - (in ~85% of the patients)
  - +/- Post-operative EBRT if unexpected risk factors appeared following the operation
Ipsilateral breast tumour recurrence

- Pre-pathology
  2.1% IORT versus 1.1% EBRT \((p = 0.31)\)
Randomized multicenter clinical trial confirmed that Targeted Intraoperative Radiotherapy (TARGIT) with INTRABEAM is non-inferior (as good as) to External Beam Radiotherapy (EBRT).

3451 Patients were randomized in 33 centers from 11 countries between 2000 and 2012.

Patients with no Local Recurrence in the Ipsilateral Breast at 5 Years

<table>
<thead>
<tr>
<th>Arm</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>EBRT Control Arm</td>
<td>98.9 %</td>
</tr>
<tr>
<td>TARGIT Study Arm</td>
<td>97.9 %*</td>
</tr>
</tbody>
</table>

\[ p = 0.31 \]

*Prepathology stratum: TARGIT concurrently with lumpectomy is similar as EBRT
Breast Cancer Mortality

Overall, breast cancer mortality was much the same between groups (3.3% [1.9–5.8] for TARGIT* vs 2.7% [1.5–4.6] for EBRT; p=0.72)

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<table>
<thead>
<tr>
<th>TARGIT</th>
<th>3.3%</th>
</tr>
</thead>
<tbody>
<tr>
<td>EBRT</td>
<td>2.7%</td>
</tr>
</tbody>
</table>

*prenpathology
Non-Breast Cancer Deaths

There were significantly fewer non-breast-cancer deaths with TARGIT* (1.3% [0.7–2.8] vs 4.4% [2.8–6.9]; p=0.016), attributable to fewer deaths from cardiovascular causes and other cancers.

*prepathology
Overall Mortality

Overall mortality was 4.6% (1.8–6.0) for TARGIT* versus 6.9% (4.3–9.6) for EBRT (p=0.123).

*prepathology
Complications

Grade 3 or 4 skin complications

- TARGIT: 4 of 1720
- EBRT: 13 of 1731

p = 0.029
Quality of Life

Radiation-related quality of life parameters after targeted intraoperative radiotherapy versus whole breast radiotherapy in patients with breast cancer: results from the randomized phase III trial TARGIT-A

*Radiation Oncology* 2013, 8:9  doi:10.1186/1748-717X-8-9

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Quality of Life

Results

Patients receiving IORT alone reported less general pain (21.3 points), breast (7.0 points) and arm (15.1 points) symptoms, and better role functioning (78.7 points) as patients receiving EBRT (40.9; 19.0; 32.8; and 60.5 points, respectively, $P < 0.01$). Patients receiving IORT alone also had fewer breast symptoms than TARGIT-A patients receiving IORT followed by EBRT for high risk features on final pathology (IORT-EBRT; 7.0 versus 29.7 points, $P < 0.01$). There were no significant differences between TARGIT-A patients receiving IORT-EBRT compared to non-randomized IORT-boost or EBRT-boost patients and patients receiving EBRT without a boost.

Conclusions

In the randomized setting, important radiation-related QoL parameters after IORT were superior to EBRT. Non-randomized comparisons showed equivalent parameters in the IORT-EBRT group and the control groups.
Controversy

- Cochrane database of systematic reviews on partial breast radiation
  - July 2016 [www.cochranelibrary.com](http://www.cochranelibrary.com) BE Hickey
  - 7 Randomised controlled trials
    - ELIOT (intra operative electrons)
    - GEC-ESTRO, Polgar 2007 (brachytherapy)
    - Livi 2015, RAPID, Rodriguez, (EXBT)
    - TARGIT
  - n = 7586

- Problem with review of many different techniques, different patient groups (unsuitable)
Cochrane “conclusions”

- Local recurrences and elsewhere recurrences are increased – *small difference*
- Cosmesis and fibrosis may be worse but acute skin side effects less
- No difference other oncology outcomes
  - Cause specific survival
  - Distant metastasis free survival
  - Relapse free survival
  - Locoregional recurrence free survival
  - Mastectomy rates
- Limited data means.. “cannot make definitive conclusions about efficacy and safety” ..
“Position paper techniques and technologies in radiation oncology – 2015 Horizon scan”

“It is the faculty view that this technology is not supported by sufficient evidence to form a definitive view...if this device is to be used patients need to be informed that follow up is relatively short and longer follow up is required...”

NICE (UK) have approved intrabeam for selected patients in NHS hospitals
So what do our patients actually want?

- Patient preference for intra-operative or external beam radiotherapy following breast conservation
- Trade-off technique in pts BCS and awaiting EBRT or past patients.
- 64% pt opted for IORT even if there was an increased risk of local recurrence
- Risk accepted was mean of 3.2%

Alvarado, M et al Cancer Research: December 15, 2010; Volume 70, Issue 24, Supplement 2
Informed consent and patient choice

- Intrabeam
  - Selected patients
    - Short FU (5yrs data)
    - Slightly increased LR
      - *Not TARGIT data*
    - Slightly increased fibrosis
      - *Not TARGIT data*
    - Reduced acute S/E
    - Less dose to ‘normal tissues’ eg lung, heart
    - “one stop shop”
    - 20Gy single treatment
    - Less impact on daily life (time, $$)

- EXBT
  - All patients
    - LONG FU (30 yrs)
    - Good local control
    - Some fibrosis
    - Increased acute S/E
    - Higher doses to ‘normal tissues’ eg lung heart
    - Multiple visits
    - 40-50Gy in 15-25 treatments
    - Significant impact on daily life (time, $$)
Intrabeam Equipment
The X-Ray Source

Produces 50 kV x-rays
Electrons strike a gold target
Dose-depth distribution – spherical dose distribution
The delivery of IORT

- 50KV x-rays
- Standard operating theatre
- The radiation is delivered to the tissue from inside the tumour cavity
- 20Gy at surface
- 5 Gy at 10mm
- The treatment time 15 to 40min
What is involved?

- Rad Onc, Surgeon and Physicist
- SNB performed – needs to be negative
- WLE - Intra-op specimen x-ray
- Measure cavity and select the correct size applicator
The procedure

- Applicator is snug up against the cavity
- Ultrasound – distance from applicator to skin to avoid skin necrosis
- Radiation delivered 15-40 min
After procedure

- Normal surgical recovery
- Doxycycline 100mg daily 7-10 days
- Follow up 7-10 days later for full pathology
- Decision if additional external beam radiation required
  - Lymphovascular invasion
  - Metastases to sentinel node after full sectioning
  - Positive margins – re excise and deliver EXBT
So why does it work?
IORT impacts on the microenvironment

Human Cancer Biology

Targeted Intraoperative Radiotherapy Impairs the Stimulation of Breast Cancer Cell Proliferation and Invasion Caused by Surgical Wounding

Barbara Belletti,1 Jayant S. Vaidya,7 Sara D’Andrea,1 Frank Entschladen,8 Mario Roncadin,3,6 Francesca Lovat,1 Stefania Berton,1 Tiziana Perin,4 Ezio Candiani,2 Sonia Reccanello,3 Andrea Veronesi,5,6 Vincenzo Canzonieri,4 Mauro G. Trovò,3 Kurt S. Zanenker,8 Alfonso Colombatti,1 Gustavo Baldassarre1,6 and Samuele Massarut2,6
Belletti et al - IORT impacts on the microenvironment

- Wound fluid from pt treated with BCS alone and pt treated with BSC + IORT
- Cultured the wound fluid with breast cancer cells
- The wound fluid from pts that did not have IORT stimulated proliferation, migration and invasion of the breast cancer cells
So what are the concerns with IORT using Intrabeam?

- Pre-pathology setting only
- Recurrence rates are high if given post pathology
- 15% to 20% of patients will have adverse factors on the pathology and will require EBRT as well
  - May increase local fibrosis (up to 35%)
  - May increase fat necrosis
- Increase in the rate of recurrent seromas – 1% versus 2%
Intrabeam in public health system

- MoH commission Deloitte to do an economic assessment in Dec 2016
- Immature data, needs further follow up
- “On the assumption of clinical equivalence, investing in IORT in the publicly funded radiation therapy centres ..would be likely to present cost savings for the New Zealand health system and society compared to the existing EBRT services, provided that estimated demand for IORT service is sufficiently high”
- Estimated 77 women in Christchurch would fulfil criteria
Intrabeam in New Zealand

- Focus Radiotherapy, Auckland
- Patients selected as per TARGIT indications
- n=150 patients since August 2013
- EXBT rate is 12%
- 2 patients with second in breast recurrence
  - In other breast quadrants ie new primaries
- Funded by ‘all’ insurance companies EXCEPT Southern Cross (patient pays IORT component, SX pay for the operative component)
Intrabeam in Christchurch

- Equipment installed at Southern Cross Hospital
  - Control computer, dose meter
  - Applicators
  - Robotic arm

- Xray unit will travel from Auckland as required

- Local surgeons and South Island surgeons can potentially treat patients in Christchurch

- Training undertaken by surgeons, radiation oncologists and physicists completed

- Final logistics being organised ...
Ultimately it is about carefully selecting patients informed consent patient choice