Intraoperative radiotherapy in early breast cancer

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Introduction - Anatomy
Introduction – Radiotherapy

• Important in treatment of breast cancer
• 3 anatomic regions
  – Breast – Chest wall
  – Axilla
  – Other areas of draining lymphatics
Introduction – Radiotherapy

• Virtual simulation

• Dose and fractionation
  – Standard: 1.8 - 2 Gy daily (5-5.5 weeks, total dose: 45-50 Gy)
  – Alternative schedule: 42.5 Gy in 16 fractions (3 weeks)
Introduction – IORT

• Entire therapeutic dose into a single fraction

  Surgery and radiation completed in one day

• Reduced treatment visits by delivering single radiotherapy fraction immediately
• Radiotherapy accessible to patients living far from a radiotherapy center
• No treatment delay for patients who must also undergo chemotherapy
• Operative bed is visualized immediately
• Probability of missing the target is minimized in oncoplastic BCS
• Shielding of surrounding organs performed
• Potential further reduction in healthcare costs

• Increased operating times
• Lack of final pathological results before delivering IORT

  *Increased local recurrence rates compared with conventional EBRT in two RCTs*

• Staff training and operating room equipment efforts
• Expensive devices

Vaidya, TARGIT-A RCT, Lancet 2014
Veronesi, ELIOT RCT: Lancet Oncol, 2013
Intraoperative radiotherapy in early breast cancer

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Background: Intraoperative radiotherapy (IORT) constitutes a paradigm shift from the conventional 3–5 weeks of whole-breast external beam radiotherapy (EBRT). IORT enables delivery of radiation at the time of excision of the breast tumour, targeting the area at highest risk of recurrence, while minimizing excessive radiation exposure to healthy breast tissue. The rationale for IORT is based on the observation that over 90 per cent of local recurrences after breast-conserving surgery occur at or near the operation site.

Methods: This article reviews trials of IORT delivered with different techniques and devices.

Results: IORT is a very attractive option for delivering radiotherapy, reducing the traditional fractionated treatment to a single fraction administered at the time of surgery. IORT has been shown to be associated with reduced toxicity and has several potential benefits over EBRT. Only two randomized clinical trials have been published to date. The TARGIT-A and ELIOT trials have demonstrated that IORT is associated with a low rate of local recurrence, although higher than that after EBRT (TARGIT-A: 3-3 versus 1-3 per cent respectively, P = 0.042; ELIOT: 4-4 versus 0-4 per cent, P < 0.001). However, the local recurrence rate for IORT fell within the predefined 2-5 per cent non-inferiority margin in TARGIT-A, and the 7-5 per cent equivalence margin in ELIOT.

Conclusion: Longer follow-up data from existing trials, optimization of patient criteria and cost-effectiveness analyses are needed. Based on the current evidence, IORT can be offered as an alternative to EBRT to selected patients within agreed protocols, and outcomes should be monitored within national registries.

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Introduction

• Adjuvant whole-breast external beam radiotherapy (EBRT)
  – Post breast-conserving surgery (BCS)
    — reduction of local recurrence
    — improvement of survival
    Local recurrence rate (LRR): 1% - 4-7%
  – Additional boost 10-16 Gy tumour bed
    — Additional reduction of LRR by 40 %

Clarke M, Lancet 2005
Bartelink, J Clin Oncol, 2007
Introduction

• Timing
  – Delay +8 weeks postoperatively
    → Increase LRR at 5y (odds ratio 1.62, 95% CI 1.21 -2.16)

• Hypofractionated RT
  – UK 2 studies (IMORT – FAST trial)

• Accelerated partial breast irradiation (APBI) techiques
  → 90 % of local recurrences after BCS at or near the operation site

Clark, Int J Radiat Oncol Biol Phys, 1982
Fisher, Semin Surg Oncol, 1992
Introduction

- Accelerated partial breast irradiation (APBI) techniques
  - 90% of local recurrences after BCS at or near the operation site
  - Tumor foci + 4cm beyond index lesion: 7-9% in ME
  - Margin of 10 mm → 90% covering after Local excison + APBI

References:
- Clark, Int J Radiat Oncol Biol Phys, 1982
- Veronesi, N engl J Med, 1993
- Fisher, Semin Surg Oncol, 1992
- Holland, Cancer, 1985
- Vicini, Int J Radiat Oncol Biol Phys, 2004
Introduction

- Accelerated partial breast irradiation (APBI) techniques
  - Methods:
    - Multicatheter brachtherapy
    - Intracavitary balloon brachytherapy
    - Three-dimensional conformal radiotherapy
    - Intraoperative radiotherapy (IORT)
      - + : Accurate delivery
Methods

• Literature databases (up to August 2014)
  – MEDLINE
  – PubMed
  – The Cochrane Library Controlled Trials Register
  – Embase
  – UK National Research register and National Institutes of Health ClinicalTrials.Gov
Results

• Intraoperative radiotherapy by low-energy X-rays
• Intraoperative electron beam radiation therapy
• Memorial Sloan-Kettering Cancer Center technique using high-dose-rate afterloading
• Noval techniques and hybrid devices
  – Balloon catheters
  – Intraoperative avidination for radionuclide treatment
Results

- **Intraoperative radiotherapy by low-energy X-rays**
  - Low-energy X-rays (Intrabeam device)
    - Spherical application
    - 20-45 min
    - 20Gy surface
    - 5-6Gy at a depth of 1cm
Results

• **Intraoperative radiotherapy by low-energy X-rays**
  
  - *Increased local recurrence rates compared with conventional EBRT in two RCTs*

  - TARGIT – A trial 2232 patients (Lancet, 2014)
    - 2010: Median FU: 25 mo 1,2% vs 1,0% (p= 0,41)
      » -: short FU
    - 2013: Median FU: 29 mo (3451, additional 1219 patients)
      » **5Y risk of LR: 3,3% vs 1,3% (p: 0,042)**
      » -: median FU 29 mo: below median time when breast recurrences can be expected (+ more than 90% ER +)
      » Mortality: no difference (1,9 vs 2,6% (p=0,56))

  - TARGIT- B trial
    - TARGGeted Intraoperative radiotherapy – Boost (TARGIT – B) trial
    - Hypothesis: IORT boost > EBRT boost
Results

• Intraoperative radiotherapy by low-energy X-rays
• Intraoperative electron beam radiation therapy
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• Noval techniques and hybrid devices
  – Balloon catheters
  – Intraoperative avidination for radionuclide treatment
Intraoperative radiotherapy versus external radiotherapy for early breast cancer (ELIOT): a randomised controlled equivalence trial

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Summary

Background Intraoperative radiotherapy with electrons allows the substitution of conventional postoperative whole breast irradiation with one session of radiotherapy with the same equivalent dose during surgery. However, its ability to control for recurrence of local disease required confirmation in a randomised controlled trial.

Methods This study was done at the European Institute of Oncology (Milan, Italy). Women aged 48–75 years with early breast cancer, a maximum tumour diameter of up to 2.5 cm, and suitable for breast-conserving surgery were randomly assigned in a 1:1 ratio (using a random permuted block design, stratified for clinical tumour size [<1.0 cm vs 1.0–1.4 cm vs ≥1.5 cm]) to receive either whole-breast external radiotherapy or intraoperative radiotherapy with electrons. Study coordinators, clinicians, and patients were aware of the assignment. Patients in the intraoperative radiotherapy group received one dose of 21 Gy to the tumour bed during surgery. Those in the external radiotherapy group received 50 Gy in 25 fractions of 2 Gy, followed by a boost of 10 Gy in five fractions. This was an equivalence trial; the prespecified equivalence margin was local recurrence of 7.5% in the intraoperative radiotherapy group. The primary endpoint was occurrence of ipsilateral breast tumour recurrences (IBTR); overall survival was a secondary outcome. The main analysis was by intention to treat. This trial is registered with ClinicalTrials.gov, number NCT01849133.

Findings 1305 patients were randomised (654 to external radiotherapy and 651 to intraoperative radiotherapy) between Nov 20, 2000, and Dec 27, 2007. After a medium follow-up of 5.8 years (IQR 4.1–7.7), 35 patients in the intraoperative radiotherapy group and four patients in the external radiotherapy group had had an IBTR (p=0.0001). The 5-year event rate for IBTR was 4.4% (95% CI 2.7–6.1) in the intraoperative radiotherapy group and 0.4% (0.0–1.0) in the external radiotherapy group (hazard ratio 9.3 [95% CI 3.3–26.3]). During the same period, 34 women allocated to intraoperative radiotherapy and 31 to external radiotherapy died (p=0.59). 5-year overall survival was 96.8% (95% CI 95.3–98.3) in the intraoperative radiotherapy group and 96.9% (95.5–98.3) in the external radiotherapy group. In patients with data available (n=464 for intraoperative radiotherapy; n=412 for external radiotherapy) we noted significantly fewer skin side-effects in women in the intraoperative radiotherapy group than in those in the external radiotherapy group (p=0.0002).

Interpretation Although the rate of IBTR in the intraoperative radiotherapy group was within the prespecified equivalence margin, the rate was significantly greater than with external radiotherapy, and overall survival did not differ between groups. Improved selection of patients could reduce the rate of IBTR with intraoperative radiotherapy with electrons.
Results
Results

- **Intraoperative electron beam radiation therapy (IOERT)**
  - Electron beams: limited penetration, rapid delivery

**ELIOT trial**  Veronesi, Lancet Oncol 2013

- FU 5.8 Y - + 30-45 min – 1305 patients
- LRR 4.4% vs. 0.4% (p <0.001)
- HR for development of LR: 9.3: IOERT compared with EBRT
  - subgroup: +2cm: >4 + nodes, Gr III, ER - : 5Y LRR: +10%
  - suitable and low-risk group: < 2%
  - Survival 5y: no difference

**Conclusion:** IOERT: only in carefully selected low-risk patients.

**Opm. exclusion criterium:** > 75 y
Results

• Intraoperative radiotherapy by low-energy X-rays
• Intraoperative electron beam radiation therapy
• Memorial Sloan-Kettering Cancer Center technique using high-dose-rate afterloading
• Noval techniques and hybrid devices
  – Balloon catheters
  – Intraoperative avidination for radionuclide treatment
Results

- Memorial Sloan-Kettering Cancer Center technique using high-dose-rate afterloading
  - Own IORT protocol
  - High dose rate afterloader

+: personalized applicator
-: cosmetic complications!

Pilot study:
  - 52 low risk women
  - 68 mo FU
  - LRR: 7.7%
Results

• Intraoperative radiotherapy by low-energy X-rays
• Intraoperative electron beam radiation therapy
• Memorial Sloan-Kettering Cancer Center technique using high-dose-rate afterloading
• Noval techniques and hybrid devices
  – Balloon catheters
  – Intraoperative avidination for radionuclide treatment
Discussion

Table 3  Key trials employing single-fraction intraoperative radiotherapy

<table>
<thead>
<tr>
<th>Study</th>
<th>Study type</th>
<th>No. of patients</th>
<th>Mean age (years)</th>
<th>Tumour size (cm)</th>
<th>Node status</th>
<th>Dose (Gy)</th>
<th>Device</th>
<th>Median follow-up (years)</th>
<th>Local recurrence (%)</th>
<th>Overall survival (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TARGIT-A</td>
<td>Phase III</td>
<td>3451</td>
<td>63</td>
<td>≤ 3.5</td>
<td>N0 – 1</td>
<td>20</td>
<td>Intrabeam®</td>
<td>2–4</td>
<td>3–3</td>
<td>96.1</td>
</tr>
<tr>
<td>ELIOT</td>
<td>Phase III</td>
<td>1305</td>
<td>57</td>
<td>&lt; 2.5</td>
<td>N0 – 2</td>
<td>21</td>
<td>Novac7®</td>
<td>5–8</td>
<td>4–4</td>
<td>96.8</td>
</tr>
<tr>
<td>UNC</td>
<td>Phase II</td>
<td>53</td>
<td>63</td>
<td>&lt; 3</td>
<td>N0</td>
<td>15</td>
<td>Mobetron®</td>
<td>3–4</td>
<td>15–1</td>
<td>94</td>
</tr>
<tr>
<td>Verona®</td>
<td>Phase II</td>
<td>226</td>
<td>63</td>
<td>≤ 5</td>
<td>N0 – 1</td>
<td>10–8</td>
<td>Mobetron®</td>
<td>3–8</td>
<td>0–4</td>
<td>100</td>
</tr>
<tr>
<td>MSKCC®³⁷,³⁸</td>
<td>Pilot</td>
<td>52</td>
<td>76</td>
<td>≤ 2</td>
<td>N0</td>
<td>18–20</td>
<td>H.A.M.®</td>
<td>5–8</td>
<td>7–7</td>
<td>86</td>
</tr>
</tbody>
</table>

TARGIT-A, TARGe ted Intraoperative radiotherapy – Alone; ELIOT, Electron IntraOperative Treatment; UNC, University of North Carolina; MSKCC, Memorial Sloan-Kettering Cancer Center; H.A.M., Harrison-Anderson-Mick applicator for high-dose-rate intraoperative radiotherapy.

Table 4  Devices approved for intraoperative radiotherapy

<table>
<thead>
<tr>
<th>Device</th>
<th>Source</th>
<th>Dose at surface (Gy)</th>
<th>Dose at 1 cm depth</th>
<th>Applicator</th>
<th>Treatment time (min)</th>
<th>Time added to surgery (min)</th>
<th>FDA and CE mark approval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Novac7®</td>
<td>Electrons at 3–9 MeV</td>
<td>21</td>
<td>3 MeV</td>
<td>Perspex tube</td>
<td>2</td>
<td>30–45</td>
<td>FDA/CE</td>
</tr>
<tr>
<td>Mobetron®</td>
<td>Electrons at 4–12 MeV</td>
<td>15–16–8</td>
<td>4–5 MeV</td>
<td>Solid tube</td>
<td>2</td>
<td>30–45</td>
<td>FDA/CE</td>
</tr>
<tr>
<td>Intrabeam®</td>
<td>50-kV X-rays</td>
<td>20</td>
<td>5–6 Gy</td>
<td>Solid sphere</td>
<td>20–45</td>
<td>30–45</td>
<td>FDA/CE</td>
</tr>
<tr>
<td>Xoft®/Ex®</td>
<td>50-kV X-rays</td>
<td>20</td>
<td>9–10 Gy</td>
<td>Balloon catheter</td>
<td>17–26</td>
<td>30–50</td>
<td>FDA/CE</td>
</tr>
<tr>
<td>HDR afterloading system</td>
<td>¹⁸²Ir</td>
<td>18</td>
<td>&lt; 10 Gy</td>
<td>H.A.M.® Silastic® disc</td>
<td>20–40</td>
<td>Up to 60</td>
<td>FDA/CE</td>
</tr>
</tbody>
</table>

*Data for intraoperative radiotherapy; Xoft® can also be used for intracavitary brachytherapy. FDA, Food and Drug Administration; CE, Conformité Européenne – European Conformity; HDR, high-dose-rate.
Discussion

• Balloon devices:
  + cheaper and easily manageable
  - Poor shape conformance and inadequate skin to balloon distance
  - Lack of clinical data when used as single fraction

• IOERT:
  – expensive equipment, investment in equipment and staff training
Discussion

• “Country-specific cost-effectiveness analysis of IORT treatments is required and should be expressed in terms of incremental cost per quality-adjusted life-year, considered from an NHS and personal social services perspective”
Discussion

IORT (Intrabeam) currently being considered for approval by the NICE Multiple Technology Appraisal draft guidance: option for patients with early breast cancer
Discussion

• TARGIT-A and ELIOT
  Historical benchmarks: 6-7.5%
  Recurrence rates below 6-7.5%
  0.375% difference in mortality at 15y
  No effect in mortality when the difference in recurrence rate is less than 10%

Published evidence supports Intrabeam
Conclusion

• IORT can be offered as an alternative to EBRT to selected patients
5-year results of accelerated partial breast irradiation using sole interstitial multicatheter brachytherapy versus whole-breast irradiation with boost after breast-conserving surgery for low-risk invasive and in-situ carcinoma of the female breast: a randomised, phase 3, non-inferiority trial


Summary
Background In a phase 3, randomised, non-inferiority trial, accelerated partial breast irradiation (APBI) for patients with stage 0, I, and II breast cancer who underwent breast-conserving treatment was compared with whole-breast irradiation. Here, we present 5-year follow-up results.

Methods We did a phase 3, randomised, non-inferiority trial at 16 hospitals and medical centres in seven European countries. 1184 patients with low-risk invasive and ductal carcinoma in situ treated with breast-conserving surgery were centrally randomised to either whole-breast irradiation or APBI using multicatheter brachytherapy. The primary endpoint was local recurrence. Analysis was done according to treatment received. This trial is registered with ClinicalTrials.gov, number NCT004462519.

Findings Between April 20, 2004, and July 30, 2009, 551 patients had whole-breast irradiation with tumour-bed boost and 633 patients received APBI using interstitial multicatheter brachytherapy. At 5-year follow-up, nine patients treated with APBI and five patients receiving whole-breast irradiation had a local recurrence; the cumulative incidence of local recurrence was 1.44% (95% CI 0.51-2.38) with APBI and 0.923% (0.12-1.73) with whole-breast irradiation (difference 0.523%, 95% CI -0.72 to 1.75; p=0.42). No grade 4 late side-effects were reported. The 5-year risk of grade 2–3 late side-effects to the skin was 3.2% with APBI versus 3.7% with whole-breast irradiation (p=0.08), and 5-year risk of grade 2–3 subcutaneous tissue late side-effects was 7.6% versus 6.3% (p=0.53). The risk of severe (grade 3) fibrosis at 5 years was 0.2% with whole-breast irradiation and 0.8% with APBI (p=0.46).

Interpretation The difference between treatments was below the relevance margin of 3 percentage points. Therefore, adjuvant APBI using multicatheter brachytherapy after breast-conserving surgery in patients with early breast cancer is not inferior to adjuvant whole-breast irradiation with respect to 5-year local control, disease-free survival, and overall survival.

Funding German Cancer Aid.

Introduction Breast cancer is the most common cancer diagnosed in women in Europe. Previous uncertainties about the role of adjuvant radiation therapy after breast-conserving surgery have been clarified after publication of whole-breast irradiation compared with mastectomy alone, up to 50% of patients in the USA who are clinically qualified for breast conservation still undergo mastectomy with the goal to omit radiation therapy. One of the most important reasons for us is the ability of breast-conserv