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Miami Beach, FL USA

State-of-the-Art:
The Optimal Means of Delivering
Accelerated Partial Breast Irradiation (APBI)

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Disclosures

• Non-salaried Consultant for Nucletron/Elekta

• Recipient of an Unrestricted Educational/Research Grant from Elekta to Conduct a 6-Institution Registry Trial of Interstitial Brachytherapy APBI

• Cianna Medical: minor stock options

APBI: The Concept

• Accelerated partial breast irradiation (APBI) is a 5-day or less alternative to conventional 5-7 weeks of external beam whole breast irradiation (WBI)

• Substantial pathology and clinical data demonstrates that residual cancer cells after a lumpectomy with clear margins are within 1-2 cm of the surgical cavity edge

• Remote in-breast recurrence in the other quadrants is rare (3-5%), and may be excluded from high-quality breast imaging (e.g. MRI) before the treatment
APBI: The Concept

- The extended time for WBI is difficult for many busy, modern women.
- Patients and their doctors wish to minimize exposure of normal tissues (heart, lung, skin, chest wall, lymphatics, uninvolved breast).
- These issues inspired us 22 years ago to investigate a treatment that only covers the involved portion of the breast, lasts one week or less, with minimal collateral damage.
- Our original hypothesis: “Brachytherapy is the ideal choice for such a treatment.”

APBI Early Clinical Trials

- The initial New Orleans trial (Ochsner Clinic) and the Michigan trial (Wm Beaumont Hospital) have reported 7-10 year data supporting the hypothesis of brachytherapy APBI.
- RTOG 95-17 phase II trial of interstitial brachytherapy, now out 12.5 years, has demonstrated a very low 4.2% isolated breast recurrence rate with broad selection criteria (e.g. node +).
- The Hungarian phase III trial is positive for brachytherapy, since tumor control was equivalent with better cosmesis in the brachy arm over WBI.
RTOG 95-17: Interstitial Brachy w/12.5 yrs FU

Long-term outcome from RTOG 9517: A phase III study of accelerated partial breast irradiation (APBI) with multivolumewhitetet Brachytherapy (MCT) following lumpectomy for early-stage breast cancer.

5 and 10 year Estimates of Ipsilateral In-breast Recurrence, Regional Nodal Recurrence and Contralateral Breast Cancer

<table>
<thead>
<tr>
<th>5 year</th>
<th>10 year</th>
</tr>
</thead>
<tbody>
<tr>
<td>#</td>
<td>(%)</td>
</tr>
<tr>
<td>In-breast recurrence</td>
<td>4</td>
</tr>
<tr>
<td>In field</td>
<td>3</td>
</tr>
<tr>
<td>Out of field</td>
<td>1</td>
</tr>
<tr>
<td>In-breast &amp; Regional recurrence</td>
<td>2</td>
</tr>
<tr>
<td>ALL In-breast recurrences</td>
<td>6</td>
</tr>
<tr>
<td>ISOLATED Regional recurrence</td>
<td>3</td>
</tr>
</tbody>
</table>
APBI Later Clinical Trials

- Large phase III trials from North America (NSABP B39/RTOG 0413 with 4214 patients) and GEC-ESTRO are maturing after closure and should be published in 2-3 years
- IORT phase III trials (TARGit-UK, ELIOT-Milan)
- Overall, > 12 phase III APBI clinical trials
- More patients in one trial (NSABP/RTOG) than all randomized clinical trials that took us from mastectomy to breast conservation with WBI

APBI: Successors to Interstitial Brachy

- Simplifying APBI with single-entry balloon catheters or a strut-based device has been reported in large registry trials

- Disappointing pre-treatment path review, dosimetry, quality assurance, and clinical outcomes has plagued intraoperative radiotherapy with Intrabeam or electron beam
Milan IORT Randomized Phase III Trial

Intraoperative radiotherapy versus external radiotherapy for early breast cancer (ELIOT): a randomised controlled equivalence trial

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 45–75 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 cm or 1–2–3–4 cm] or ≥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 study.

Milan IORT Conclusions

• “The rate of IBTR was significantly higher with electron IORT over WBI, although the Survival rates did not differ.”

• Better selection criteria for IORT may improve these results
TARGIT-A Trial: Soft x-ray IORT vs. WBI

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 Rubens, Jeffrey S. Tolikas, David J. Hopwood, Mohammed Karchgar, Henrik J. Fryget, Samuelu Massot, Michael Alverado, Christofel Saunders, Wolfgang Eiermann, Marinos Metaxa, Elena Speck, Max Stüßer, Douglas Brown, Enrico Sceven, Mario Roncalli, Richard Thompson, John A. Brewer, Helle M. Hleibing, Staff Sigrist, Mary Faleiro, Eleanor Harris, April Mathews, Chiara Paoletti, James W. Baudet, Alfredo Biezman, and Staff of the TARGIT-A randomised group

Summary

Background The TARGIT-A trial compared risk-adapted radiotherapy using single-dose targeted intraoperative radiotherapy (TARGIT) versus fractionated external beam radiotherapy (EBRT) for breast cancer. We report 5-year results for local recurrence and the first analysis of overall survival.

Methods TARGIT-A was a randomised, non-inferiority trial. Women aged 45 years and older with invasive ductal carcinoma were enrolled and randomly assigned in a 1:1 ratio to receive TARGIT or whole-breast EBRT, with blocks stratified by centre and by timing of delivery of targeted intraoperative radiotherapy; randomisation occurred either before lumpectomy (prepathology stratum: TARGIT concurrent with lumpectomy) or after

TARGIT Outcomes Graphs

The results of a comparison of cumulative incidence for local recurrence in the presence of competing risks (death and withdrawal from trial) were no different from Kaplan-Meier estimates, showing that these risks did not bias the main results (data not shown).

Analysis limited to the mature cohort, first reported in 2010 (n=2332, median follow-up now 3 years 7 months), in which most events had occurred (32 of 34 local recurrences and 85 of 86 deaths), yielded much the same results (data not shown).

Table 3 shows the Z-score and p-value for the primary outcome of local recurrence in the conserved breast, for the whole cohort, the mature cohort, and the earliest cohort. Non-inferiority is established for the whole cohort and for prepathology patients but not for postpathology patients.

Figure 4 shows the primary (local recurrence in the conserved breast) and secondary outcomes (death) for the prepathology stratum. It shows the differences in 5-year estimates for these outcomes for the whole cohort.
APBI Options: IORT vs. Brachytherapy

• The data for brachytherapy is favorable with long-term follow-up, and more aggressive tumors are allowed (grade 3, endocrine receptor negative, Her-2 +, node +, etc.)

• The data for IORT seems to be deteriorating over time with less aggressive tumors (grade 1-2, ER +, Her-2 -, smaller node -)

Secrets?

Who keeps secrets!
Secrets?

Who keeps secrets!

The Secret to High Quality Breast Brachytherapy
The Secret to High Quality Breast Brachytherapy

• Is image-guidance

And

• Exquisite ability
  to shape the radiation dose cloud
Interstitial Brachytherapy Registry Study

Interstitial Multi-catheter Brachytherapy for Breast Cancer: a Multi-institutional Study

Mitchell Kamrava, MD, Robert R. Kuske, MD, FAACE, Peter Chen, MD, John Hayes, MD, Bethany Anderson, MD, Coral Quiet, MD, Pin-Chieh Wang, PhD, Darlene Veruttipong, BS, Margaret Snyder, RN and D. Jeffrey Demanes, MD.

- **Objective:** To report outcomes for breast cancer treated with breast-conserving therapy using accelerated partial breast irradiation (APBI) with interstitial multi-catheter brachytherapy by a cooperative group of institutions.

Interstitial Brachytherapy Registry Study: Results

- 849 pts in the first ABS report (>1500 in the final analysis)
- Median follow-up of 4.3 years (range 0.003-20.9)
- The 5 year actuarial risk of an ipsilateral breast tumor recurrence was 3% for all patients (3.8% for DCIS, 3% for IDC, 0% for ILC, and 3.8% for other)
- 34/849 (4.0%) Crude rate of local recurrence
- Elsewhere failures in 26/34 (76%) cases, marginal misses in 5/34 (15%) cases, and true recurrences in 3/34 (9%) cases.

{Study supported by an unrestricted educational/research grant from Elekta}
NSABP B39/RTOG 0413: 6 weeks vs. 5 days

• While the first publication is not expected for 2-3 years (data ripening on the vine), the statisticians have not noted a difference between the arms sufficient to release the outcomes early (early stopping rules)

• 70% 3dCRT, 25% single entry, 5% interstitial

• 4214 patients entered exceeds the total number in 7 randomized trials of BCT vs MRM
APBI: Current Arizona Selection Criteria

• APBI appears to be an acceptable option for treatment of select tumors < 3 cm

• Excised with clear margins

• With 0-3 + nodes without extracapsular extension