Single Institution experience with hypofractionated simultaneous integrated boost using volumetric modulated arc therapy and extending its indications for DCIS

FIORENZA DE ROSE MD
RADIATION ONCOLOGY
Humanitas Research Hospital, Rozzano (Milan)
• Breast-conserving surgery and radiation is a standard alternative to mastectomy for most patients with early stage breast cancer (stage I-II)

• Conventional radiation fractionation of 1.8-2 Gy per day is delivered in 6-7 weeks of treatment
Hypofractionated WBI: Why?

THE RADIOBIOLOGIC ISSUE

• Breast cancer has an alpha/beta ratio for tumor control of 4.6 (larger fraction sizes maximize local control in tumor tissue)
• Radiobiologic models show that increasing fraction size with a large reduction of the total radiation dose can keep late toxicity comparable to that seen with conventional fractionation
• Moreover, the reduction of treatment time (3/4 weeks) reduces the possibility of tumor cells to repair the radiation injury

QiXS, White J, LiXA. Is α/β for breast cancer really low? Radiother Oncol. 2011;100:282-288
Hypofractionation of WBI: When?
Hypofractionated WBI: Which?

Table 1 Four prospective phase 3 randomized trials of hypofractionated WBI versus conventional fractionation in early-stage breast cancer

<table>
<thead>
<tr>
<th>Trial</th>
<th>Years conducted</th>
<th>n</th>
<th>Fractionation Gy/n of fractions</th>
<th>Local recurrence,%</th>
<th>Good/excellent cosmesis,%</th>
<th>Time point</th>
</tr>
</thead>
<tbody>
<tr>
<td>RMH/GOC</td>
<td>1986–1998</td>
<td>470</td>
<td>50/25</td>
<td>12.1</td>
<td>71</td>
<td>10 years</td>
</tr>
<tr>
<td>[7, 8]</td>
<td></td>
<td>466</td>
<td>42.9/13</td>
<td>9.6</td>
<td>74</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>474</td>
<td>39/13</td>
<td>14.8</td>
<td>58</td>
<td></td>
</tr>
<tr>
<td>START A</td>
<td>1998–2002</td>
<td>749</td>
<td>50/25</td>
<td>3.6</td>
<td>60^a</td>
<td>5 Years</td>
</tr>
<tr>
<td>[9]</td>
<td></td>
<td>750</td>
<td>41.6/13</td>
<td>3.5</td>
<td>58^a</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>737</td>
<td>39/13</td>
<td>5.2</td>
<td>66^a</td>
<td></td>
</tr>
<tr>
<td>START B</td>
<td>1999–2001</td>
<td>1105</td>
<td>50/25</td>
<td>3.3</td>
<td>61^a</td>
<td>5 Years</td>
</tr>
<tr>
<td>[10•]</td>
<td></td>
<td>1110</td>
<td>40/15</td>
<td>2.2</td>
<td>66^a</td>
<td></td>
</tr>
<tr>
<td>OCOG</td>
<td>1993–1996</td>
<td>612</td>
<td>50/25</td>
<td>6.7</td>
<td>71</td>
<td>10 Years</td>
</tr>
<tr>
<td>[11•]</td>
<td></td>
<td>622</td>
<td>42.5/16</td>
<td>6.2</td>
<td>70</td>
<td></td>
</tr>
</tbody>
</table>

... Whole-breast dose of 40 Gy delivered in 15 fractions is gentler on normal tissues than conventional regimen without evidence of inferior local tumor control ...

Hypofractionated WBI: OPEN ISSUES

Tumor bed boost

- The use of tumor bed boost reduced the risk of local recurrence even in patients with negative resection margins.

- Few data to define the indications for and toxicity of tumor bed boost in patients treated with hypofractionated WBI.


Hypofractionationed WBI: OPEN ISSUES
Tumor bed boost

<table>
<thead>
<tr>
<th>Trial</th>
<th>Accrued</th>
<th>Median F/U (yr.)</th>
<th>Fractionation of Whole breast fractionation</th>
<th>Lumpectomy volume Fractionation</th>
<th>In-breast recurrence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Formenti [40]</td>
<td>91</td>
<td>1</td>
<td>2.7 Gy × 15 = 40.5 Gy</td>
<td>3.2 Gy × 15 = 48 Gy</td>
<td>0</td>
</tr>
<tr>
<td>Teh [47]</td>
<td>15</td>
<td>1</td>
<td>2.65 Gy × 16 = 42.2 Gy</td>
<td>3.28 Gy × 16 = 52.48 Gy</td>
<td>0</td>
</tr>
<tr>
<td>Cante [44]</td>
<td>463</td>
<td>2.3</td>
<td>2.25 Gy × 20 = 45 Gy</td>
<td>2.75 Gy × 20 = 55 Gy</td>
<td>0</td>
</tr>
<tr>
<td>Morganti [48]</td>
<td>201</td>
<td>2.6</td>
<td>2.5 Gy × 16 = 40 Gy</td>
<td>2.75 Gy × 16 = 44 Gy</td>
<td>0</td>
</tr>
<tr>
<td>Corvo [45]</td>
<td>377</td>
<td>3</td>
<td>2 Gy × 25 = 50 Gy</td>
<td>2.4 Gy × 25 = 60 Gy</td>
<td>0</td>
</tr>
<tr>
<td>Ciervide [41]</td>
<td>145</td>
<td>5</td>
<td>2.3 Gy × 20 = 46 Gy</td>
<td>3.5 Gy × 5 = 52 Gy</td>
<td>0</td>
</tr>
<tr>
<td>Freedman [43]</td>
<td>75</td>
<td>5.8</td>
<td>2.8 Gy × 15 = 42 Gy</td>
<td>3.3 Gy × 15 = 49.5 Gy</td>
<td>4.1%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2.75 Gy × 15 = 40.5 Gy</td>
<td>3.2 Gy × 15 = 48 Gy</td>
<td>2.7%</td>
</tr>
</tbody>
</table>
Hypofractionated WBI: OPEN ISSUES
Ductal Carcinoma in situ

• There are few published data evaluating the effectiveness of hypofractionated RT in DCIS

• The role of additional RT to the surgical bed in patients with DCIS has not been studied in phase III trials

Clinical Investigation

Hypofractionated Radiation Therapy for Breast Ductal Carcinoma In Situ

Lara Hathout, MD, * Tarek Hijal, MD, † Valérie Théberge, MD, ‡§ Bernard Fortin, MD, *
Horia Vulpe, MD, † Jean-Charles Hogue, MD, §‡ Christine Lambert, MD, † Houda Bahig, MD, *
Louise Provencher, MD, §‖ Peter Vavassis, MD, * and Michael Yassa, MD*
Phase I-II study of hypofractionated simultaneous integrated boost using volumetric modulated arc therapy for adjuvant radiation therapy in breast cancer patients: a report of feasibility and early toxicity results in the first 50 treatments

Marta Scorsetti\textsuperscript{1}, Filippo Alongi\textsuperscript{1*}, Antonella Fogliata\textsuperscript{2}, Sara Pentimalli\textsuperscript{1}, Pierina Navarra\textsuperscript{1}, Francesca Lobefalo\textsuperscript{1}, Carlos Garcia-Etienne\textsuperscript{3}, Alessandro Clivio\textsuperscript{2}, Luca Cozzi\textsuperscript{2}, Pietro Mancosu\textsuperscript{1}, Giorgia Nicolini\textsuperscript{2}, Eugenio Vanetti\textsuperscript{2}, Marco Eboli\textsuperscript{3}, Carlo Rossetti\textsuperscript{3}, Arianna Rubino\textsuperscript{3}, Andrea Sagona\textsuperscript{3}, Stefano Arcangeli\textsuperscript{1}, Wolfgang Gatzemeier\textsuperscript{3}, Giovanna Masci\textsuperscript{4}, Rosalba Torrisi\textsuperscript{4}, Alberto Testori\textsuperscript{5}, Marco Alloisio\textsuperscript{5}, Armando Santoro\textsuperscript{4} and Corrado Tinterri\textsuperscript{3}
Characteristics of the STUDY

• This is a phase I-II prospective non-randomized trial of adjuvant radiotherapy with simultaneous integrated boost (SIB) delivered with RapidArc technology.

• The study was approved by the internal ethical committee and patient consent was obtained.

• The study will include 450 patients with a total period of 10 years of follow-up.
Characteristics of the study: OBJECTIVES

• **Primary endpoint** of the study is to evaluate the feasibility of VMAT and hypofractionation with simultaneous integrated boost in breast cancer patients at early stage and undergoing conservative surgery.

• **Secondary endpoint** of the study is the evaluation of toxicity in terms of acute and late side effects.

• It will also be assessed the local control, even if it is not an explicit objective of the study.
The study is still recruiting patients: here we present the preliminary data of toxicity and clinical assessment of the first 252 patients.

Eligibility criteria were:
- age >18 years
- invasive cancer or DCIS
- American Joint Committee on Cancer AJCC Stage I to II
- breast-conserving surgery
- any systemic therapy
Patients were in supine position, with both arms above the head.

CT dataset was acquired with 3 mm thick adjacent slices.

No respiratory gating was adopted.
Characteristics of the study: PLANNING DETAILS
Characteristics of the study: PLANNING DETAILS
Characteristics of the study: PLANNING DETAILS
Skin toxicity was visually assessed by objective clinical exam and pictures of irradiated breast during each visit (during treatment and during follow-up).

Acute skin toxicities were recorded according to RTOG scoring criteria.

Late skin toxicities were recorded according to CTCAE v4.0.

Cosmetic outcomes were assessed as excellent/good or fair/poor.
Characteristics of the study: CLINICAL RESULTS

- Median follow up of 22 months
- All patients were scored as excellent/good (252/252) compared with baseline
- 3 cases of recurrences, all of them out of RT fields

Skin Toxicity during treatment

Skin Toxicity after treatment

- Pre RT
- End of RT
- Follow up @ 90 days
Skin clinical results: comparison with literature

<table>
<thead>
<tr>
<th></th>
<th>Dose Gy</th>
<th>n. fr</th>
<th>G1</th>
<th>G2</th>
<th>G3</th>
<th>G4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scorsetti et al.2012</td>
<td>40.5/48</td>
<td>15</td>
<td>64%</td>
<td>0</td>
<td>2%*</td>
<td>0%</td>
</tr>
<tr>
<td>Formenti et al.2006</td>
<td>40.5/48</td>
<td>15</td>
<td>58%</td>
<td>8%</td>
<td>1%</td>
<td>0%</td>
</tr>
<tr>
<td>Freedman et al.2007</td>
<td>45/56</td>
<td>20</td>
<td>65%</td>
<td>23%</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>Chada et al. 2012</td>
<td>40.5/45</td>
<td>15</td>
<td>96%  (Go+G1)</td>
<td>4%</td>
<td>0%</td>
<td>0%</td>
</tr>
</tbody>
</table>

*1 case of G3= bilateral irradiation
CONCLUSIONS

- The 3-week course of postoperative radiation using VMAT with SIB showed to be well tolerated in acute and early late setting and was associated with optimal local control.

- Long-term follow-up data are needed to assess late toxicity and clinical outcomes.
THANKS FOR YOUR ATTENTION