TARGIT: Review of clinical evidence for breast cancer – Why INTRABEAM in Breast cancer?

Dr. Brigitte Both

February 4th and 5th, 2016
Breast cancer: figures and facts

- Breast cancer is the most common type of cancer in women worldwide and is diagnosed in **1.3 million women** each year\(^1\)
- Tendenz steigend mit ca. 2 Millionen in 2050

- **Nearly 460,000** will die from the disease, making it second to lung cancer as leading cause of death for women\(^1\)

- Still **26 - 35 %** of Breast-Conserving Surgery patients do not pursue follow-up radiotherapy according to an analysis\(^2\)

- **80 – 90 %** of breast cancer cases are eligible for IORT with INTRABEAM as single treatment or boost\(^4\)

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Therapy Options with IORT

IORT as a definitive dose (TARGIT-A Trial)

IORT as a boost

IORT for patients where EBRT is not an option

Re-IORT for recurrent breast cancer

Nipple Sparing Mastectomy

300 centres are treating patients with INTRABEAM worldwide
Breast cancer is frequently multicentric …

But most recurrences occur near the primary tumour.

So, it is the goal to target radiotherapy to the tumour bed.

**Rationale for IORT**

**Multicentricity of breast cancer: whole-organ analysis and clinical implications**

JS Vaidya¹, JJ Vyas², RF Chinoy³, N Merchant⁴, OP Sharma⁵ and I Mittra⁶

Departments of ¹Surgical Oncology, ²Pathology, ³Radiology. Tata Memorial Hospital, Bombay, 400 012, India.
IORT Treatment

University Heidelberg, Mannheim

Targeted Intraoperative Radiotherapy (TARGIT)

Prof. Dr. med. Marc Sütterlin
Professor and Chairman
Department of Obstetrics and Gynaecology
University Medical Center Mannheim, University of Heidelberg

Prof. Dr. med. Frederik Wenz
Professor and Chairman
Department of Radiation Oncology
University Medical Center Mannheim, University of Heidelberg
Clinical studies

IORT as a definite dose (TARGIT-A Studie)

TARGIT-A is currently the largest multicenter randomized clinical trial in the field of Partial Breast Irradiation. (>1200 Patienten FU 5Y, study start 2000)
Clinical Trials

IORT as a definitive dose (TARGIT-A Trial)

Predefined stratification according to the time of TARGIT delivery

1. Immediate delivery (also referred as pre-pathology stratum)

   Step 1
   Breast Conserving Surgery (BCS) and immediate TARGIT

   Patient leaves the hospital

   LRR | P
   ---|---
   Pre-Pathology | |
   EBRT | 1.1% | 0.31
   IORT | 2.1% | |

   Post-Pathology
   EBRT | 1.7 | 0.069
   IORT | 5.4% | |

2. Delayed delivery (also referred as post-pathology stratum)

   Step 1
   Breast Conserving Surgery (BCS)

   Patient leaves the hospital

   Step 2
   Final Pathology

   Step 3
   Delayed TARGIT in a second procedure

   1 Day
   days / weeks

Clinical studies

IORT as definite dose (TARGIT-A Studie)

Overall mortality

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.

*Trephathology
Clinical studies

IORT as definitive dose (TARGIT-A Studie)

Overall mortality

<table>
<thead>
<tr>
<th></th>
<th>TARGIT</th>
<th>EBRT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Other cancers</td>
<td>8</td>
<td>16</td>
</tr>
<tr>
<td>Cardiovascular causes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiac*</td>
<td>2</td>
<td>8</td>
</tr>
<tr>
<td>Stroke</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Ischaemic bowel</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Other†</td>
<td>7</td>
<td>8</td>
</tr>
<tr>
<td>Total</td>
<td>17</td>
<td>35</td>
</tr>
</tbody>
</table>

5-year risk 1-4% for TARGIT versus 3-5% for EBRT; log-rank p=0.0086.
TARGIT = targeted intraoperative radiotherapy. EBRT = external beam radiotherapy.
*Included one “sudden death at home” in EBRT group. †TARGIT: two diabetes, one renal failure, one liver failure, one sepsis, one Alzheimer’s disease, one unknown; EBRT: one myelopathy, one perforated bowel, one pneumonia, one old age, four unknown.

Table 2: Causes of death other than breast cancer in all patients

Clinical Trials

IORT as a definitive dose (TARGIT-A Trial)

Factors for the lower recurrence rates in the stratum with immediate Targit $^{1,2}$:

- Immediate delivery of radiation to well vascularised tissues at the right time
- Immediate placement of the radiotherapy applicator directly in the fresh tumour bed has beneficial effects on cytokines$^{1,2}$
- Sterilisation on the tumour microenvironment and wound fluid

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Table 1. WF proteins altered by TARGIT

<table>
<thead>
<tr>
<th>Decreased by TARGIT</th>
<th>Increased by TARGIT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Angiogenin</td>
<td>AgRP</td>
</tr>
<tr>
<td>Fgf3 ligand</td>
<td>EGFR</td>
</tr>
<tr>
<td>Il-10</td>
<td>FAS/TNFRSF6</td>
</tr>
<tr>
<td>Il-6</td>
<td>FGFR-4</td>
</tr>
<tr>
<td>Il-7</td>
<td>G-CSF</td>
</tr>
<tr>
<td>Leptin</td>
<td>IGFBP-6</td>
</tr>
<tr>
<td>Mcp-1</td>
<td>Ii-13</td>
</tr>
<tr>
<td>Mcp-2</td>
<td>Il-4</td>
</tr>
<tr>
<td>Rantes</td>
<td>Il-5</td>
</tr>
<tr>
<td>Pdgf-Bb</td>
<td>Mip-1d</td>
</tr>
<tr>
<td>Gro</td>
<td></td>
</tr>
<tr>
<td>Hgf</td>
<td></td>
</tr>
<tr>
<td>Il-8</td>
<td></td>
</tr>
<tr>
<td>Mip-1a</td>
<td></td>
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<tr>
<td>Stnfr-II</td>
<td></td>
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<tr>
<td>Stnfr-I</td>
<td></td>
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<tr>
<td>Upar</td>
<td></td>
</tr>
<tr>
<td>VEGF-R3</td>
<td></td>
</tr>
<tr>
<td>Tie-1</td>
<td></td>
</tr>
<tr>
<td>Tie-2</td>
<td></td>
</tr>
</tbody>
</table>

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Survival without local recurrence

Figure 2. Survival without local recurrence
This Kaplan-Meier plot is the true representation of how patients with breast cancer would fare in the first 5 years of their life following treatment with TARGIT during lumpectomy or EBRT, with respect to local control. Censoring is done at the point of last follow up or withdrawal. For any patient her chance of being alive without local recurrence can be read off this plot.
The 5-year survival without local recurrence:
TARGIT: 93.9% (95%CI 90.9 – 95.9)  EBRT: 92.5% (95%CI 89.7 – 94.6), p value = 0.35.
Survival without local recurrence

What happened to women with early breast cancer, treated with TARGIT during lumpectomy compared with those treated with EBRT, over the first 5 years?

1000 women randomised to TARGIT

- 939 women alive without local recurrence
- 20 women alive after treatment of local recurrence
- 1 woman died after local recurrence
- 40 women died

1000 women randomised to EBRT

- 925 women alive without local recurrence
- 10 women alive after treatment of local recurrence
- 1 woman died after local recurrence
- 64 women died

There was no statistically significant difference in survival without local recurrence

1 dot = 1 woman

TARGIT-A international multi-centre trial included 3451 women randomised to receive TARGIT or EBRT. These figures are created by applying 5-year Kaplan-Meier estimates of survival without local recurrence to 1000 women having breast conserving therapy in the two trial arms. Distant or regional disease not shown: there was no difference seen between TARGIT and EBRT.
Comparison: Targit vs. GEC-ESTRO Study

GEC-ESTRO: - 2.2 % LRR
- AHT 90%
- 0% N+

TARGIT prepath: - 2.1 % LRR
-AHT not mandatory
- 15% N+

Strnad et al.: The Lancet Published Online October 20, 2015
## Additional evidence

<table>
<thead>
<tr>
<th>Study</th>
<th>Study Size</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elliott et al (2012)</td>
<td>n=67 breasts treated</td>
<td>post-operative cosmesis acceptable</td>
</tr>
<tr>
<td>(USA) [4]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Deneve et al (2012)</td>
<td>n=42 breasts treated</td>
<td>related toxicity acceptable</td>
</tr>
<tr>
<td>(USA) [2]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grobmyer et al (2013)</td>
<td>n=80 breast in n=78 women treated</td>
<td>majority of patients had good to excellent cosmesis, procedure was well tolerated and toxicities appeared to be low;</td>
</tr>
<tr>
<td>(USA) [3]</td>
<td></td>
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<tr>
<td>Tuschy et al. (2013)</td>
<td>patients treated in the TARGIT trial, n=147 women treated with IORT as a boost and n=61 patients treated with IORT as a single method of treatment</td>
<td>no severe postoperative complications, observed acute toxicity after IORT was low, no differences with regard to short term complications between the two groups were observed;</td>
</tr>
<tr>
<td>(Germany) [5]</td>
<td></td>
<td></td>
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<tr>
<td>Merdad et al (2013)</td>
<td>n=45 patients treated (IORT alone or IOER followed by EBRT)</td>
<td>none of the patients developed clinically significant complications, cosmetic outcome was at least acceptable in all patients;</td>
</tr>
<tr>
<td>(Saudi Arabia) [6]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Keshtgar et al. (2013)</td>
<td>subgroup of patients included in TARGIT trial</td>
<td>superior cosmetic outcome for TARGIT patients when compared with patients treated with EBRT, differences between IORT and EBRT patients more significant at the beginning of the follow-up</td>
</tr>
<tr>
<td>[7]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kolberg et al. (2013)</td>
<td>n=200 patients treated</td>
<td>satisfaction with cosmetic outcome 92% (patients) and 95% (physicians);</td>
</tr>
<tr>
<td>(Germany) [8]</td>
<td></td>
<td></td>
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<tr>
<td>Jankiewicz et al. (2013)</td>
<td>Treatment with IORT alone (n=19) or IORT followed by EBRT (n=61)</td>
<td>No serious complications prolonging hospitalization; 5-year overall and disease free survival 100% in IORT group and 95,1% and 96,7%, respectively, in the IORT plus EBRT group, excellent and good aesthetic outcome in 90% of the patients</td>
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<tr>
<td>(Poland) [9]</td>
<td></td>
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<tr>
<td>Steiner et al. (2013)</td>
<td>n=400 patients treated</td>
<td>Mild to moderate local complications in 14,5%</td>
</tr>
<tr>
<td>(Israel) [10]</td>
<td></td>
<td>Major complications in 6,2%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ipsilateral breast failures in 1,7%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Systemic disease in 1%</td>
</tr>
<tr>
<td>Abbott et al. (2015)</td>
<td>n=100 patients treated</td>
<td>Wound infection rates were low for both groups. Two LR occurred (both patients R70). Median follow-up time was 24 months</td>
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</tbody>
</table>
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
Grit Welzel (grit.welzel@umm.de)
Anja Roth (anja.roth@umm.de)

30 minutes

35 visits

Less pain

Original article
Persistent pain after targeted intraoperative radiotherapy (TARGIT) or external breast radiotherapy for breast cancer: A randomized trial

Kenneth Geving Andersen a,b,†, Rune Görtner c, Niels Kroman c, Henrik Flyger d, Henrik Kehlet a

a Section for Surgical Pathophysiology, Rigshospitalet, University of Copenhagen, Denmark
Our results from 81 patients show that the majority of breast cancer patients will accept a small increment of local risk for a simpler delivery of radiation.

The mean additional accepted risk for IORT was 3.2%
Most Western Australian health professionals working with breast cancer patients are willing to accept an increase in risk of local recurrence in order to replace EBRT with IORT in a hypothetical setting.
Wound-related complications were much the same between groups but grade 3 or 4 skin complications were significantly reduced with TARGIT
Better cosmetic results

Objective assessment of cosmetic outcome after targeted intraoperative radiotherapy in breast cancer: results from a randomised controlled trial

Mohammed R. S. Keshtgar • Norman R. Williams • Max Bulsara • Christobel Saunders • Henrik Flyger • Jaime S. Cardoso • Tammy Corica • Neils Bentzon • Nikolaos V. Michalopoulos • David J. Joseph

Conclusion:

Signifikant better cosmetic results
TARGIT vs EBRT
Avoid risk of secondary cancer

Review

Risk of second non-breast cancer after radiotherapy for breast cancer: A systematic review and meta-analysis of 762,468 patients

Trine Grantzau *, Jens Overgaard

Department of Experimental Clinical Oncology, Aarhus University Hospital, Denmark

ABSTRACT

Background and purpose: Radiotherapy for breast cancer both decreases loco-regional recurrence rates and improves overall survival. However, radiotherapy has also been associated with increased second cancer risk at exposed sites. In this meta-analysis, we estimated the risk of second non-breast cancers after radiotherapy for breast cancer.

Material and methods: The databases Medline/Pubmed, Cochrane, Embase and CMAH were systematically searched, for cohort studies on second cancer after radiotherapy for breast cancer, from inception to August 1st 2013. Included studies were to report the relative risk (RR) of second cancers comparing irradiated female breast cancer patients to unirradiated patients. Primary end points were all second non-breast cancers and second cancers of the bone, lungs, thyroid and skin.

Can the risk of secondary cancer induction after breast conserving therapy be reduced using intraoperative radiotherapy (IORT) with low-energy x-rays?

Muhammad Hammad Aziz1,2, Frank Schneider1, Sven Clausen1, Elena Blank1, Carsten Herskind1, Muhammad Afzal2 and Frederik Wenz1*
Side effects on the cardiovascular system

Risk of Ischemic Heart Disease in Women after Radiotherapy for Breast Cancer

Sarah C. Darby, Ph.D., Marianne Ewertz, D.M.Sc., Paul McGale, Ph.D., Anna M. Bennet, Ph.D., Ulla Blom-Goldman, M.D., Dorthe Brennum, R.N., Candace Correa, M.D., David Cutter, F.R.C.R., Giovanna Gagliardi, Ph.D., Bruna Gigante, Ph.D., Maj-Britt Jensen, M.Sc., Andrew Nisbet, Ph.D., Richard Peto, F.R.S., Kazem Rahimi, D.M., Carolyn Taylor, D.Phil., and Per Hall, Ph.D.

CONCLUSIONS

Exposure of the heart to ionizing radiation during radiotherapy for breast cancer increases the subsequent rate of ischemic heart disease. The increase is proportional to the mean dose to the heart, begins within a few years after exposure, and continues for at least 20 years. Women with preexisting cardiac risk factors have greater absolute increases in risk from radiotherapy than other women. (Funded by Cancer Research UK and others.)

Figure 3 Cumulative DVH for ipsilateral lung and heart for IORT, APBI and EBRT.

DVH: Dose volume histrograme
Therapy Options with IORT

- IORT as a definitive dose (TARGIT-A Trial)
- IORT as a boost
- IORT for patients where EBRT is not an option
- Re-IORT für Patientinnen bei Rezidiv
- Nipple Sparing Mastectomy

Worldwide patients are treated in 300 centres.
LONG-TERM RESULTS OF TARGETED INTRAOPERATIVE RADIOOTHERAPY (TARGIT) BOOST DURING BREAST-CONSERVING SURGERY


Jayant S Vaidya¹, Michael Baum¹, Jeffrey S Tobias¹, Frederick Wenz², Samuele Massarut³, Mohammed Keshtgar¹, Basil Hilaris⁴, Christobel Saunders⁵, Norman R Williams¹, Chris Brew-Graves¹, Tammy Corica⁵, Mario Roncadin³, Uta Kraus-Tiefenbacher², Max Bulsara⁵, David Joseph⁵

UNITED KINGDOM ¹University College London, GERMANY ²Radiation Oncology, University of Mannheim, ITALY ³Surgery and Radiation Oncology, CRO, Aviano, USA ⁴Radiation Oncology, Our Lady of Mercy Medical Center, New York, AUSTRALIA ⁵Surgery and Radiation Oncology, Sir Charles Gairdner Hospital, Perth
Clinical studies

IORT as Boost

Table 2B. High-risk factors compared with EORTC and START-B trial

<table>
<thead>
<tr>
<th>High-risk factors</th>
<th>EORTC boost</th>
<th>START-B trial</th>
<th>Target boost</th>
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<tbody>
<tr>
<td>Young age</td>
<td>33% were ≤50</td>
<td>21% were &lt;50</td>
<td>32% were ≤50</td>
</tr>
<tr>
<td>% &gt;1 cm</td>
<td>75%</td>
<td>86%</td>
<td>78%</td>
</tr>
<tr>
<td>% Grade 3</td>
<td>Not available</td>
<td>23%</td>
<td>29%</td>
</tr>
<tr>
<td>% Node +</td>
<td>21%</td>
<td>23.6%</td>
<td>29%</td>
</tr>
<tr>
<td>Recurrence rate at 5 years</td>
<td>4.3%</td>
<td>2.8%</td>
<td>1.73%</td>
</tr>
</tbody>
</table>

Abbreviations: EORTC = European organization for research and treatment of cancer; START-B = standardisation of breast radiotherapy study.
LONG-TERM TOXICITY OF AN INTRAOPERATIVE RADIOTHERAPY BOOST USING LOW ENERGY X-RAYS DURING BREAST-CONSERVING SURGERY


UTA KRAUS-TIEFENBACHER, M.D.,* LELIA BAUER, M.D.,† ANTONELLA SCHEDA, M.D.,*
KATHARINA FLECKENSTEIN, M.D.,* ANKE KELLER,* CARSTEN HERSKIND, PH.D.,*
VOLKER STEIL, M.SC.,* FRANK MELCHERT, M.D.,† AND FREDERIK WENZ, M.D.*

Departments of *Radiation Oncology and †Gynecology and Obstetrics, Mannheim Medical Center, University of Heidelberg, Mannheim, Germany

Clinical studies

IORT als Boost
Clinical studies

IORT as Boost

Results

Fig. 1. Cosmetic evaluation after 6, 12, 18, 24, and 36 months on a score of 1 to 4. One patient with a poor cosmetic result was treated with mastectomy because of marked fibrosis of the entire breast 12 months after intraoperative radiotherapy (IORT), and 1 patient was evaluated as having “fair” cosmetic outcome during further follow-up.


Carl Zeiss Meditec AG, Dr. Brigitte Both, Director Medical and Health Economy
Matched pair Analyse

Intraoperative versus external beam boost for breast cancer: A matched-pair analysis

Elena Sperk, Daniela Astor, Grit Welzel, Axel Gerhardt*, Marc Sütterlin*, Frederik Wenz

Overall Survival matched pair analysis n = 53

90.2% vs. 62.3%, p = 0.375

Conclusions

IORT given as a boost seems to have a positive impact on overall survival in breast cancer patients after breast conserving surgery. To identify such an effect a prospective randomized trial should be conducted.

J Clin Oncol 31, 2013 (suppl; abstr 1120)
Sub-Analysis of Targit A

Fewer non-breast cancer deaths in the TARGIT-A trial: Systemic benefit of TARGIT or lack of EBRT toxicity

Jayant S Vaidya1, Max Bulsara2, Frederik Wenz3, Samuele Massarut4, David Jones5, Jeffrey S Tobias1, Norman Williams1, Michael Baum1;
1London UK, 2Fremantle AU, 3Mannheim DE, 4Aviano IT, 5Perth AU,
on behalf of the TARGIT Trialists’ Group

Conclusion

- With the caveat of small numbers, there is no difference in cardiac deaths by tumour laterality
- The risk of cardiac death appears to be similar to an age matched population
- TARGIT+EBRT had significantly fewer non-breast cancer deaths than EBRT (p=0.012)
- Therefore, avoidance of EBRT toxicity may not completely explain the significant reduction in non-breast cancer deaths in the TARGIT arm of the randomised trial.

http://www.oncoletter.ch/index.tpl?rubrik=738
Is timing important for radiation?

✓ **Immediacy** (no temporal miss) (e.g. Chemotherapie, pre-path vs post path TARGIT)

✓ **Accuracy** (no geographical miss)

✓ **Acitivity**
  ✓ Radio Biological Effectiveness (RBE) (single high dose vs. fractionation)
  ✓ high LET (linear energy transfer kv vs. MV)
  ✓ Change on microenvironment and wound fluid at the tumour bed
  ✓ Influence on cytokines that enhance tumor cell growth

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**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 Roncadini,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. Trovo,3 Kurt S. Zaneker,8 Alfonso Colombatti,1 Gustavo Baldassarre,1,6 and Samuele Massarut2,6

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**Relative biological effectiveness of photon energies used in brachytherapy and intraoperative radiotherapy techniques for two breast cancer cell lines**

ANNE B. L. MARTHINSEN1, RAGNHILD GISESTAD1, SIGNE DANIELSEN1, JOMAR FRENGEN1, TROND STRICKERT1 & STEINAR LUNDGREN1,2

1Department of Oncology, St. Olavs Hospital, Trondheim University Hospital, 7006 Trondheim, Norway and 2Department of Cancer Research and Molecular Medicine, Norwegian University of Science and Technology (NTNU), 7006 Trondheim, Norway

---

**Surgery-induced wound response promotes stem-like and tumor-initiating features of breast cancer cells, via STAT3 signaling**

Ilenia Segatto1, Stefania Berton1, Maura Sonego1, Samuele Massarut2, Tiziana Perin7, Erica Piccillo1, Alfonso Colombatti5, Andrea Vecchione1, Gustavo Baldassarre1 and Barbara Belletti1

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**High throughput screening of cytokines, chemokines and matrix metalloproteinases in wound fluid induced by mammary surgery**

Dan Wang1,+, Kebang Hu1,+, Ningning Gao3, Hao Zhang1, Yanlin Jiang1, Caigang Liu1, Shouyu Wang1, Zuwei Zhao1
Impact of time interval from cancer surgery to radiotherapy on local recurrence

Punglia BMJ 2010
breast conserving therapy
N = 18 050
Travel Distance to RT & Receipt of RT following Cancer Surgery

Athas J Natl Cancer Inst 2000
Recommed in Oncoplastic reconstruction

IORT as Boost

ONCOPLASTIC BREAST RECONSTRUCTION AFTER IORT


WOLFRAM MALTER M.D., VERENA KIRN, PROF. PETER MALLMANN, STEFAN KRAEMER M.D. BREAST CENTER, UNIVERSITY HOSPITAL OF COLOGNE, KERPENER STR. 34, 50931 COLOGNE, GERMANY

Conclusion:

The advantage of an oncoplastic reconstruction after breast-conserving surgery and IORT boost irradiation should be recommended to improve local outcome, to avoid seroma formation and to improve the cosmetic outcome after treatment.
Therapy Options with IORT

- IORT as a definitive dose (TARGIT-A Trial)
- IORT as a boost
- IORT for patients where EBRT is not an option
- Re-IORT for recurrence
- Nipple Sparing Mastectomy

Worldwide patients are treated in 300 centres.
IRT can be administered to patients where EBRT is not advised

21 patients had previously received EBRT
31 patients had clinical reasons such as systemic lupus erythematosus, motor neuron disease, Parkinson’s disease, ankylosing spondylitis, morbid obesity, and cardiovascular or severe respiratory disease
28 patients were included for compelling personal reasons, usually on compassionate grounds
After a median follow-up of 38 months, only two local recurrences of this 80 patients were observed, avoiding mastectomy
IORT can be used in patients wearing a cardiac pace maker

Pacemaker and radiotherapy in breast cancer: is targeted intraoperative radiotherapy the answer in this setting?

Mohammed RS Keshtgar¹, David J Eaton², Claire Reynolds², Katharine Pigott³, Tim Davidson¹, Benjamin Gauter-Fleckenstein³ and Frederik Wenz³

Intraoperative radiotherapy using the Intrabeam device was successfully used to treat an invasive ductal carcinoma of the left breast with a cardiac pacemaker located close in distance to the treatment area. This approach may form a viable alternative to conventional radiotherapy which has been shown to adversely effect such devices.
Therapy Options with IORT

IORT as a definitive dose (TARGIT-A Trial)

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IORT for patients where EBRT is not an option

Re-IORT for recurrence

Nipple Sparing Mastectomy

Worldwide patients are treated in 300 centres.
Intraoperative radiotherapy (IORT) is an option for patients with localized breast recurrences after previous external-beam radiotherapy.
A cohort analysis to identify eligible patients for intraoperative radiotherapy (IORT) of early breast cancer

Elena Sperk¹, Daniela Astor¹, Anke Keller¹, Grit Welzel¹, Axel Gerhardt², Benjamin Tuschy², Marc Sütterlin² and Frederik Wenz³

# Ongoing clinical trials

<table>
<thead>
<tr>
<th>Study</th>
<th>Application Focus</th>
<th>Goal</th>
<th>Study Lead</th>
<th>Start</th>
<th>End</th>
</tr>
</thead>
<tbody>
<tr>
<td>Targit – Korea</td>
<td>Breast Single Fraction</td>
<td>IORT for Korean Patients With Breast Cancer to assess local toxicity for Asian patients, HTA assessment for reimbursement in South Korea</td>
<td>Gangnam Severance Hospital</td>
<td>2014</td>
<td>2016</td>
</tr>
<tr>
<td>Targit – Hypofraction</td>
<td>Breast Boost</td>
<td>IORT Boost in hypofraction EBRT</td>
<td>ICO Barcelona</td>
<td>2018</td>
<td>2017</td>
</tr>
<tr>
<td>KYPHO-IORT</td>
<td>Spine</td>
<td>Combining Intraoperative Radiotherapy With Kyphoplasty For Treatment of Spinal Metastases to establish evidence</td>
<td>Loyola University</td>
<td>2015</td>
<td>2018</td>
</tr>
<tr>
<td>Targit – BQR</td>
<td>Breast Boost</td>
<td>TARGGeted Intraoperative radioTherapy With INTRABEAM as a Boost For Breast Cancer - A Quality Control Registry to implement IORT boost as preferred standard in guidelines</td>
<td>University Medical Center Mannheim</td>
<td>2012</td>
<td>2018</td>
</tr>
<tr>
<td>Targit – US</td>
<td>Breast Single Fraction</td>
<td>Efficacy and toxicity of breast radiotherapy given intra-operatively as a single fraction to enforce acceptance of Intrabeam IORT in the US and increase evidence level</td>
<td>USCF San Francisco</td>
<td>2013</td>
<td>2018</td>
</tr>
<tr>
<td>Targit, Retro, US</td>
<td>Breast Single Fraction</td>
<td>Phase IV trial, retrospective trial to assess outcome in daily practice as health service research trial to support evidence level</td>
<td>University of Cleveland</td>
<td>2013</td>
<td>2018</td>
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<tr>
<td>Targit R, UK</td>
<td>Breast Single Fraction</td>
<td>Phase IV trial, Prospective patient outcome trial provide platform for data registry in the UK and Saudi Arabia</td>
<td>NHS UK, UCL</td>
<td>2015</td>
<td>2018</td>
</tr>
<tr>
<td>Re-IORT Trial France</td>
<td>Breast Single Re-IORT Fraction</td>
<td>Feasibility Clinical Trial of Intraoperative Radiotherapy (IORT) and Second Breast-conserving-surgery After Local Recurrence of Breast Carcinoma to open further breast indication</td>
<td>Institut du Cancer de Montpellier-Val d'Aurelie</td>
<td>2015</td>
<td>2018</td>
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<tr>
<td>INTRAGO</td>
<td>Glyoblastoma</td>
<td>Establish intraoperative Glyoblastoma treatments through a randomized trial in the clinical guidelines DEGRO &amp; NICE</td>
<td>University Hospital Mannheim</td>
<td>2015</td>
<td>2019</td>
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<tr>
<td>Targit C</td>
<td>Breast Single Fraction</td>
<td>TARGIT-C(Consolidation) Prospective Phase IV Study to facilitate treatment for centers where guidelines allow treatment only within studies</td>
<td>University Medical Center Mannheim</td>
<td>2015</td>
<td>2019</td>
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<tr>
<td>Spine Metastases</td>
<td>Spine</td>
<td>Randomized study with IORT during Kypho/Vertebroplasty for Spinal Metastases to establish clinical guidelines</td>
<td>University Hospital Mannheim</td>
<td>2015</td>
<td>2019</td>
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<td>Diverse</td>
<td>Immunologic response</td>
<td>Lab study to prove hypothesis of immediacy</td>
<td>University of Barcelona</td>
<td>2015</td>
<td>2019</td>
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<tr>
<td>Targit – B</td>
<td>Breast Boost</td>
<td>Superiority of IORT boost, IORT Boost vs External Beam Radiotherapy Boost to implement IORT Boost as preferred standard in guidelines +* FU for Targit A</td>
<td>University College, London NIHR</td>
<td>2014</td>
<td>2020</td>
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<tr>
<td>Nipple sparing</td>
<td>Breast Single Fraction</td>
<td>IORT for Breast Cancer Women After NSM to prove survival benefit for countries where mastectomy is standard</td>
<td>Guangdong Academy of Medical Sciences</td>
<td>2015</td>
<td>N/A</td>
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<tr>
<td>DCIS</td>
<td>Breast Single Fraction</td>
<td>IORT After Breast-conserving Surgery in Treating Women With Ductal Carcinoma in Situ Breast Cancer to prove method as alternative to EBRT and implement in standards</td>
<td>Guangdong Academy of Medical Sciences</td>
<td>2015</td>
<td>N/A</td>
</tr>
</tbody>
</table>
Thank you for your attention

We make it visible.