

# #1039 Cosmetic outcome after *targeted intraoperative radiotherapy* (TARGIT) for early breast cancer

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## Targit - the Rationale

- **Clinicopathological rationale** 91% of local recurrence after breast conserving therapy occurs at the site of the primary tumour. Radiotherapy to the site of the original tumour may be adequate.
- **Technical rationale** Up to 50% of local recurrence may be attributable to 'geographical miss'. Accurate targeting of radiotherapy may prevent this.
- **Patient perspective** Many women are forced to choose mastectomy, just because they live far from a radiotherapy centre- so a single session of radiotherapy may allow them to benefit from breast conserving surgery.
- **Hospital perspective** This technique may free up resources for treating other cancers.
- **Economic perspective** this is new technology that may actually save money

## Targit - Pilot studies

UK, Australia, Germany, Italy, & USA to test feasibility, safety & efficacy

### Patients and methods

- Patients suitable for breast conserving surgery received wide local excision + axillary surgery followed by Targeted intra-operative radiotherapy with Intrabeam (5Gy @1cm~10Gy @0.5cm). The protocol included a single dose of peri-operative antibiotic. Most patients received post-operative whole breast radiotherapy without the tumour-bed boost.
- In Jan 2003, all available patients from the UK pilot study (median follow up 45 months) were formally assessed for cosmetic outcome including breast texture and comfort by an independent breast surgeon and nurse; they were also asked to score the breast appearance, texture and comfort and give a score for expected results.
- Satisfaction index, SI =observed/expected score was calculated.

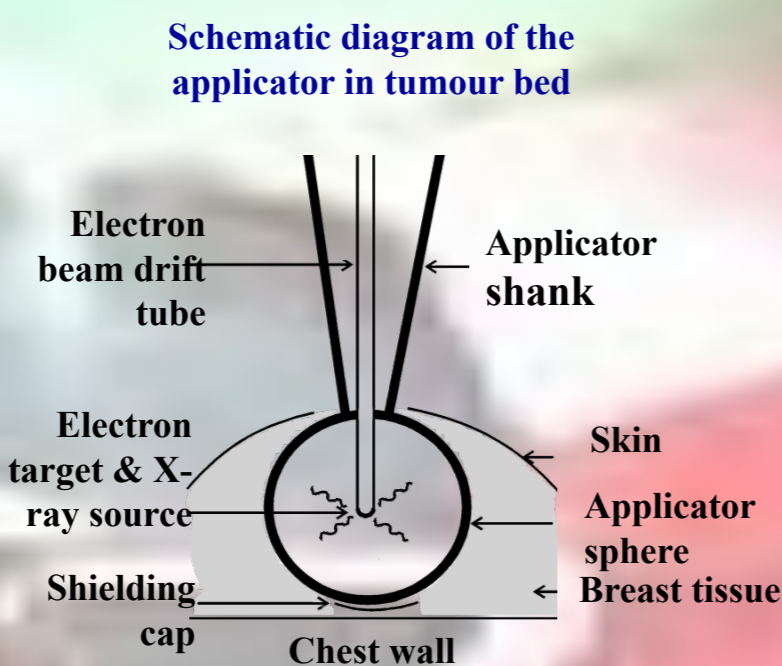
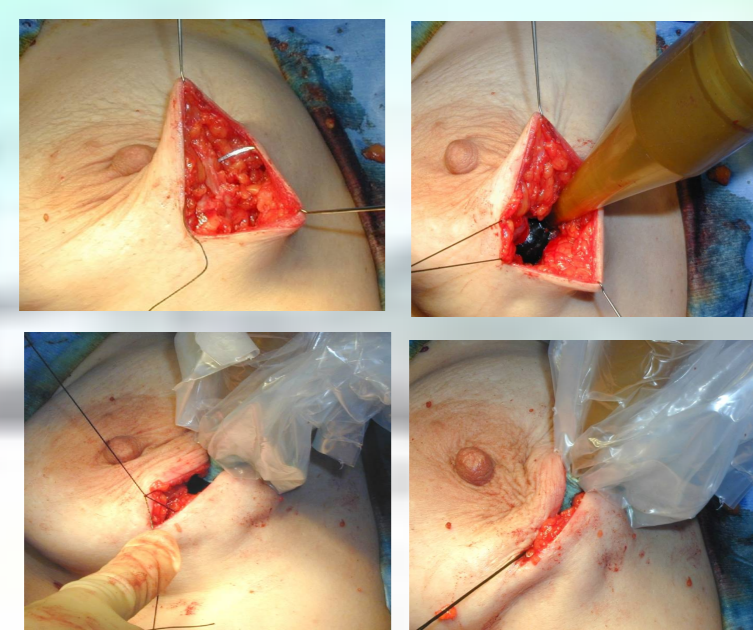
## Cosmetic results of available UK patients contd...

Satisfaction Index (Observed/Expected) – UK patients

	Mean	95%C.I.	Median
For Appearance	1.3	0.8-1.8	1
For Texture	1.3	0.8-1.7	1
For Comfort	1.3	0.8-1.8	1

- Breast appearance, texture and comfort as objectively assessed by the independent surgeon and nurse as well as by the patient were satisfactory.
- Objective assessments for appearance and texture by the independent surgeon and nurse correlated very well with the categorised assessment by the patient.
- The cosmetic outcome was at least as good, if not better (Satisfaction index =1.3) than the patients expected.

## Targit- the technique -Intrabeam™



- A miniature electron generator and accelerator that delivers *soft x-rays* (50kV) from within the breast
- The pliable breast tissue wraps around the applicator achieving true conformal brachytherapy.
- The procedure is performed in a standard operation theatre in 25-30 min

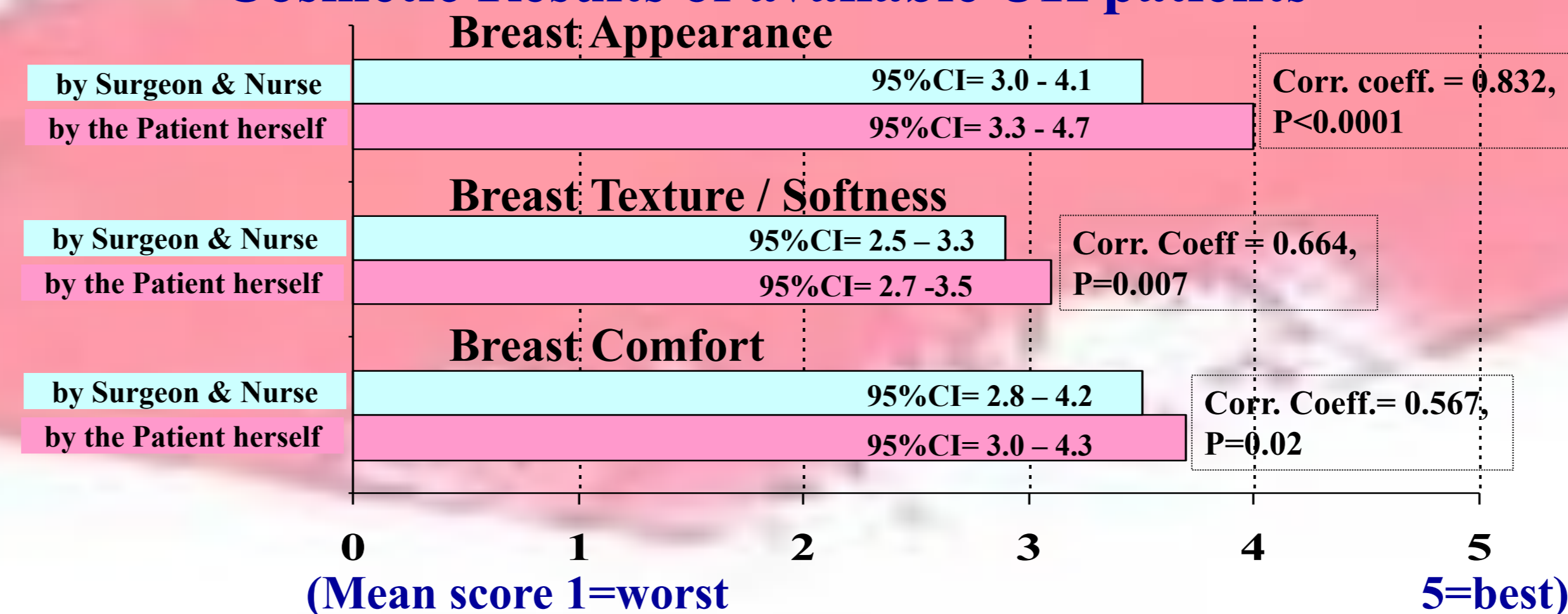
## Targit- Results of Pilot studies

- 185 patients have been treated, 22 of which received no other radiotherapy
- There has been one new primary and one diffuse local recurrence

### Follow up times of Pilot Studies

	n	median	max
UK	25	52 m	65 m
USA	57	25 m	43 m
Australia	27	18 m	30 m
Germany	50	13 m	22 m
Italy	26	10 m	16 m

## Cosmetic Results of available UK patients



## Discussion

- The satisfactory subjective and objective cosmetic results at 3.5 years after Targeted Intra-operative radiotherapy is encouraging especially since these patients have received high dose intensity as well as high total dose.
- We feel that patient's own assessment of cosmetic outcome is one that should matter; but this may be criticised as being very subjective. In this study, patients' own assessment using validated objective criteria correlated well with that of the observer. These data may well allow a more rational assessment of cosmetic outcome in randomised trials.
- The multi-centre randomised trial (TARGIT) to test whether intraoperative radiotherapy can substitute the usual 5 to 7-wk postoperative course is underway and is open for participation from interested centres.

Further Reading: [www.ctg.ucl.ac.uk](http://www.ctg.ucl.ac.uk) Correspondence: [j.vaidya@ucl.ac.uk](mailto:j.vaidya@ucl.ac.uk)  
 Intrabeam™ is manufactured by Carl Zeis Inc.



## 1038

**An estrogen receptor variant with dominant negative activity exerts beneficial influences on mammary tumor development in transgenic mice.**

Davis VL, Cline JM, Shaikh F, Hughes CL. Duquesne University, Pittsburgh, PA; Wake Forest University School of Medicine, Winston-Salem, NC; Cedars-Sinai Medical Center, Los Angeles, CA; Quintiles, Inc., Research Triangle Park, NC

Estrogen receptor (ER) variants are expressed in normal and neoplastic breast tissue, however, the roles for the variants in the breast and breast cancer have not been clearly delineated. For one variant, ERΔ3, the in-frame deletion of exon 3 from ERα results in a dominant negative receptor. The ability to inhibit ER activity suggests that ERΔ3 may provide some protection to tissues that develop hormonally responsive cancers, such as the breast. Therefore, to test if the ERΔ3 repressor could inhibit mammary tumor development, transgenic mice were generated that express the mouse ERΔ3 receptor in most tissues, including the mammary gland. The ERΔ3 mice were crossed with MMTV-*neu* (*neu*) transgenic mice that express the normal *neu* gene (*erbB2*, *HER2*). The *neu* mouse model is similar to human breast cancer, since the female mice develop primary and metastatic mammary cancer through the spontaneous activation of *c-neu*. Tumor development was assessed in bistransgenic ERΔ3/*neu* females maintained on an isoflavone-free diet until the maximum age of 16 months. The average age of mammary tumor onset was significantly delayed by 1.5 months, in the ERΔ3/*neu* females compared to *neu* females, 10.7 ± 0.3 months (n=71) versus 9.2 ± 0.3 months (n=81), p< .01. The maximal incidence was also slightly improved with 85.9% versus 95.1% of females developing tumors by age 16 months. The reduced maximal incidence is likely due to the delayed latency. (Analysis of metastatic progression is ongoing.) Since estrogen is needed to activate the dominant negative activity of ERΔ3, we wanted to determine if other estrogens with protective profiles in breast tissue might augment the influences of the ERΔ3 repressor on mammary tumor development. Tumor development was compared in ERΔ3/*neu* versus *neu* females treated with soy, plus isoflavones, and tamoxifen. Isoflavone exposure in the mice was comparable to women consuming >300 mg isoflavones/day. The dose of tamoxifen was comparable to the preventative dose used for women (20 mg/day). Both compounds were provided in the diet, based on 1800 calories (kcal)/day diet for an average woman, starting at 2 months of age. As in the ERΔ3/*neu* females on the control diet, a delayed onset of tumor development was also evident for soy isoflavones (1.1 months); however isoflavones did not augment the effect of ERΔ3. In contrast, the preventative activity of tamoxifen was enhanced in the ERΔ3/*neu* mice. In the *neu* females, tamoxifen prevented tumor development in 81% of the females, but without altering tumor latency. In the ERΔ3/*neu* females, only 1 tamoxifen-treated female developed a mammary tumor by age 16 months (98% remained tumor-free). These data suggest that expression of ERΔ3 in breast tissue may delay the onset of breast cancer induced by the most common oncogene in human breast cancer (*HER2/neu*), as well as augment the preventative capabilities of tamoxifen.

Supported by the California Breast Cancer Research Program

## 1039

**Cosmetic outcome after targeted intraoperative radiotherapy (targit) for early breast cancer.**

Vaidya JS, Wilson A, Houghton J, Tobias JS, Joseph D, Wenz F, Hilaris B, Massarut S, Keshitgar M, Sainsbury R, Taylor I, D'Souza D, Saunders C, Corica T, Ezio C, Mauro A, Baum M. Middlesex and Whittington Hospitals, University College London, London, London, United Kingdom; Middlesex Hospital, London, London, United Kingdom; Sir Charles Gairdner Hospital, Perth, Australia; Institut für Klinische Radiologie, Mannheim, Germany; Our Lady of Mercy New York Medical Centre, New York Medical College, New York, NY; Centro di Riferimento Oncologico, Aviano, Italy

Since most early local recurrences occur at the site of the primary tumour it has been suggested that breast irradiation may be limited to this site. Based on this premise, we started pilot studies in 1998, with a portable device, Intrabeam™, that delivers therapeutic radiation, intraoperatively, over 25-30 minutes. In the pilot studies, aimed at assessing safety and feasibility, patients received Targit in addition to whole breast radiotherapy. Together, the UK, US, German, Italian and

Australian centres have treated 185 patients over last 5 years with very encouraging results. The technical details, main results and of the ongoing randomised trial testing whether this approach can substitute the 6-wk postoperative radiotherapy, are presented elsewhere.

Since these patients received a large dose, albeit in a small volume, we carefully assessed the early wound healing and early and late cosmetic outcome.

Overall, there has been one case of wound breakdown attributable to radiotherapy 3 months after surgery. This was because the skin was brought too close to the applicator causing radionecrosis- we have not had such a complication after modifying the operative technique.

In Jan 2003, all available patients from the UK pilot study<sup>1</sup> (median follow up 45 months) were formally assessed for cosmetic outcome including breast texture and comfort by an independent breast surgeon and nurse; they were also asked to score the breast appearance, texture and comfort, and to give a score for 'expected' results. Satisfaction index, SI =observed/expected score was calculated.

For all scores 1=worst, 5=best	Cosmetic Results of available UK patients			
	Surgeon+ nurse (A)	According to patient (B)	Correlation between A & B	Satisfaction Index by patient (observed/ expected)
Appearance	3.5 (3.0-4.1)	4.0 (3.3 - 4.7)	0.832,p<0.0001	1.3 (0.8-1.8)
Texture/ Softness	2.9 (2.5-3.3)	3.1 (2.7 - 3.5)	0.664,p=0.007	1.3 (0.8-1.7)
Breast comfort	3.7 (3-4.3)	3.5(2.8 - 4.2)	0.567,p=0.02	1.3 (0.8-1.8)

The good cosmetic results, subjective as well as objective, at 3.5 years is reassuring. We also found the patient's own assessment correlated well with that of the observer.

A multi-centre randomised trial (TARGIT) to test whether intraoperative radiotherapy can substitute the usual 5 to 6-wk course is underway.

<sup>1</sup>Vaidya JS, Baum M, Tobias JS, Ann Oncol 2001;12:1075-80

## 1040

**ABSTRACT #1040  
WITHDRAWN**

## 1041

**Excision only for small tubular cancers of the breast.**

Leonard CE, Howell KA, Shapiro H, Ponce J, Kercher J. Rocky Mountain Cancer Centers, Littleton, CO; HealthOne Alliance, Denver, CO; Colorado Cancer Registry, Denver, CO; Arapahoe Surgical Associates, Littleton, CO

Purpose/Objective: To assess the rationale of excision only (without breast irradiation) for small tubular breast cancer.

Materials/Methods: 44 patients coded as a pure tubular invasive breast cancer who have undergone complete excision only with a minimum 1 year follow-up were identified by name from the Colorado Central Cancer Registry and assessed for local recurrence rates and disease-free/overall survivals. This was done in accordance with an initial IRB approval (12/29/98) identifying 21 patients and HIPAA regulations (23 patients from four area hospitals).

Results: Patients were treated from 11/99 to 4/01. The median age of these patients was 67 with a range of 40 to 96. The median tumor size was 6 mm with a range of 2 mm to 30 mm. All patients had a complete excision with negative margins; however, the size of the normal tissue margin was not known. 12 patients had adjuvant hormonal therapy. 3/16 patients with an axillary dissection had positive lymph nodes (all with 2 positive nodes). Staging was as follows: T1N0(11), T1Nx(27) T2N0(1), T1N1(3) - 2 were unable to be staged accurately. We did confirm that 5 patients were not treated with breast irradiation secondary to their refusal, 1 because of progressive contralateral breast cancer and 1 secondary to CREST syndrome. We did not accurately identify the reason for omitting breast irradiation in 37 patients. After a median follow-up of 5.4 years (range 1.1 to 26.3 years), there were only two local recurrences in the ipsilateral breast (at 8.8 years and 7.6 years). 13 patients died without any evidence of disease or local/distant recurrence. 2 patients experienced contralateral breast occurrences. Five and 10 year actuarial overall survival, disease-free survival and local control rates were: 100% and 87%, 100% and 91%, 100 and 87%. Both recurrences were salvaged and are currently NED at last follow-up of 13.3 years and 9 years respectively. Five and 10 year local control rates for tumors < and > 6 mms were: 100% and 69%, 100% and 100%. 25

Plenary presentation

[https://youtu.be/\\_bv8TvlH9bY](https://youtu.be/_bv8TvlH9bY)

oncogenic and growth factor signaling pathways. In addition, cyclin D1 protein is stabilized through activation of the AKT signal pathway. Recent studies have identified an important role for cyclin D1 in regulating cellular differentiation. Cyclin D1 forms physical interactions with histone acetyl transferases (P/CAF, p300, AIB1) and several transcription factors (ER $\alpha$ , AR, PPAR $\gamma$ ) which, in turn, regulate breast cellular proliferation. The accumulating evidence that cyclin D1 and cyclin E either physically interact with, or regulate the activity of histone-modifying proteins, provides important evidence for cross talk between cell cycle control and acetylation. As histone acetylases regulate the activity of diverse proteins including histone transcription factors, coactivators, and structural proteins, the abundance of these regulatory subunits may play a role in coordinating diverse metabolic processes.

### MS1-2

#### **Tumor-specific low molecular weight forms of cyclin E induce genomic instability and resistance to anti-estrogens, p21, and p27 in breast cancer.**

*Keyomarsi K, Akli S. University of Texas, MD Anderson Cancer Center, Houston, TX*

Cyclin E, a positive regulator of the cell cycle, controls the transition of cells from G1 to S phase. Deregulation of the G1-S checkpoint contributes to uncontrolled cell division, a hallmark of cancer. We have previously reported that cyclin E is overexpressed in breast cancer and such overexpression is usually accompanied by the appearance of low molecular weight (LMW) isoforms of cyclin E protein, which are not present in normal cells. Furthermore, we have shown that the expression of cyclin E low molecular weight isoforms can be used as a reliable prognostic marker for breast cancer to predict patient outcome. The tumor-specific processing of cyclin E is generated by an elastase like serine protease that cleaves the full-length form at 2 distinct sites in the amino terminus. These LMW forms have higher CDK2 kinase activity and differ in substrate specificity from the full-length cyclin E. This hyperactivity is due to more effective binding of CDK2 to the LMW forms than the full length cyclin E. We also examined the role of cyclin dependent kinase inhibitors, p21 and p27 (CKIs) in the hyperactivity of the LMW forms of cyclin E. Our analysis revealed that the full length cyclin E/CDK2 complexes could be readily inhibited by both CKIs using either Histone H1 or GST-Rb as substrates. However, the LMW cyclin E/CDK2 complexes were significantly more resistant to inhibition by the CKIs, both in vitro using purified p21 and p27, and in vivo when the CKIs were co-infected with cyclin E and CDK2. To address the biological properties of LMW cyclin E isoforms in cultured cells, we stably transfected human mammary epithelial MCF7 cells with each of the forms of cyclin E. Our results revealed that overexpressing the LMW forms of cyclin E transformed MCF7 cells from an estrogen-responsive, antiestrogen sensitive state to one in which the cells are significantly resistant to antiestrogens. The LMW forms of cyclin E can also bind and sequester p21 and p27 without being inhibited. Such deregulation of the G1/S checkpoint as induced by the LMW cyclin E also leads to genomic instability. The genetic instability and the increased resistance to endocrine therapy and cyclin dependent kinase inhibitors, provide a molecular mechanism for poor clinical outcome of breast cancer patients with high levels of LMW forms of cyclin E in their tumor.

### MS1-3

#### **Clinical development of targeted cell cycle inhibitors.**

*Swain S. National Cancer Institute, Bethesda, MD*

Data Not Provided

### MS2-1

#### **Partial breast irradiation: current status.**

*Vicini F. William Beaumont Hospital, Royal Oak, MI*

**Introduction:** Multiple phase III trials have demonstrated equivalent long-term survival between breast conserving therapy (BCT) and mastectomy in patients with early-stage breast cancer but have provided

insufficient information on the optimal volume of breast tissue requiring post-lumpectomy radiation therapy (RT).

**Materials and Methods:** Since 1993, 199 cases of early stage breast cancer were prospectively treated with radiation therapy limited to the region of the tumor bed after conservative surgery (CS) at William Beaumont Hospital (WBH), Royal Oak, Michigan. Radiation therapy was administered using interstitial brachytherapy in all cases [120 cases with low dose rate (LDR) brachytherapy and 79 with high dose rate (HDR) brachytherapy]. The LDR brachytherapy dose was 5000 cGy delivered over 96 hours and the HDR dose was 3200 cGy in 8 fractions (twice per day over 4 days) or 3400 cGy in 10 fractions (twice per day over 5 days). The clinical target volume included the lumpectomy cavity plus a 1-2 cm margin. Local-regional control, disease-free and overall survival were analyzed. Median follow-up was 65 months.

In order to compare potential differences in failure rates based upon the volume of breast tissue irradiated, results in a matched cohort of 199 patients treated with conventional whole breast RT at WBH were analyzed. Match criteria included tumor size, nodal status, patient age, margins of excision, estrogen receptor status and the use of tamoxifen.

**Results:** Five ipsilateral breast failures were observed in patients treated with partial breast irradiation (PBI). Two failures were classified as representing recurrences of the index lesion and 3 as new primaries in untreated breast tissue. The cumulative incidence of local recurrence was 1%. On matched-pair analysis, no significant differences in the rate of local recurrence were noted between patient groups based upon the volume of breast irradiated (1% in patients treated with PBI vs 1% in patients treated with whole breast RT, p=0.65). Cosmetic results were judged as good/excellent in 98% of all brachytherapy patients.

**Conclusion:** Results with brachytherapy limited to the region of the lumpectomy cavity after tumor excision provide comparable 5-year outcomes to whole breast treatment in selected patients. In recognition of the success of this work and data from other institutions, multiple other centers in the United States (US) and Europe have now started exploring this concept and several similar phase I and II studies have been initiated. In addition, other methods of delivering PBI are also being explored such as the use of the MammoSite balloon breast brachytherapy catheter approved by the US FDA in May of 2002 as well as single fraction, intra-operative radiation therapy delivered at the time of tumor excision. Currently, we are offering PBI to women as an option for the management of their breast cancer (on study) but are also exploring if the implant (which requires the temporary placement of needles or catheters in the breast) can be replaced with 3D conformal external beam RT delivered in only 5 days. Thirty-one patients have been treated and early results have been excellent.

### MS2-2

#### **Intra-operative breast radiation: the targeted intra-operative radiotherapy (Targit) trial.**

*Vaidya JS, Tobias JS, Houghton J, Joseph D, Wenz F, Hilaris BS, Massarut S, Keshtgar M, Sainsbury R, Taylor I, Corica T, Saunders C, Roncadin M, DSouza D, Baum M. University College London, London, United Kingdom; Middlesex Hospital, London, United Kingdom; Sir Charles Gairdner Hospital, Perth, Australia; University of Mannheim, Mannheim, Germany; Our Lady of Mercy Medical Center, New York Medical College, New York, NY; Centro di Riferimento Oncologico, Aviano, Italy*

Early local recurrence usually occurs at the site of the primary tumour, suggesting that it may be unnecessary to irradiate the whole breast in all patients. In 1998, we pioneered the use of targeted intra-operative radiotherapy (Targit) with a portable device, Intrabeam, that delivers 50Kv x-rays from the surface of a spherical applicator, inserted in the tumour bed. The physical dose is 20Gy at the surface of the applicator and 5Gy at 1cm depth delivered over 25-30 minutes. The estimated biological effectivity is higher by a factor of 2 - 3 in clinical analogy to radiosurgery and IORT of other body parts.

We conducted pilot studies in the UK, USA, Germany, Italy and Australia. The traditional boost dose was substituted by a single dose with Intrabeam, with the aim of assessing the safety and overall feasibility of the approach. We have treated 185 patients. At the median follow up of 22

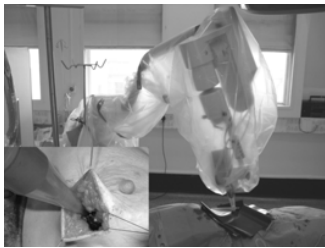
# Plenary presentation

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months, there have been 2 relapses. One recurrence in the UK cohort at 3.5 years was in a separate quadrant and the other in German cohort was diffuse at 2m. 22 patients did not have any further radiotherapy because of various reasons such as patient choice, older age, SLE, previous contralateral breast cancer. The cosmetic results are satisfactory and a formal analysis is being presented separately. We have thus found the technique to be feasible and safe.

Our ultimate aim is to test in a pragmatic randomised trial, whether Targit can effectively substitute the whole course of postoperative radiotherapy in patients with low risk of local recurrence and, by virtue of its excellent conformation (no geographical misses) improve upon the traditional boost dose in patients with high risk of local recurrence. A multi-centre randomised trial (TARGIT) is underway and is open for participation from interested centres. If found effective, Targit may be able to replace the usual 6-week course of postoperative radiotherapy and this would have significant implications for the patient and the healthcare system.

1. Vaidya JS, Baum M, Tobias JS; *Ann Oncol* 2001;12:1075-80



### MS2-3

#### Intensity-modulated breast radiotherapy: the new standard of care?

Pierce LJ, *University of Michigan, Ann Arbor, MI*

Intense research in recent years has focused upon further technical improvements in radiotherapy (RT) planning and delivery in the treatment of breast cancer. In contrast to standard RT techniques where 2-dimensional planning only optimizes dose in a single plane of the breast, emphasis has now been placed upon development of techniques to improve conformal dose delivery and homogeneity throughout the entire target volume and to further reduce RT exposure to the heart, lung, and contralateral breast. Many studies have demonstrated the superiority of 3-dimensional planning over 2-dimensional techniques with respect to improved dose homogeneity throughout the target, the ability to deliver more conformal therapy, and the ability to use dose-volume data to predict normal tissue complication probabilities. Recent studies have suggested, however, the need for further dose optimization beyond that obtained with 3-dimensional planning alone.

Further dose optimization has been achieved using a new treatment delivery technique called Intensity-Modulated Radiation Therapy (IMRT). IMRT removes the usual reliance upon flat (or uniform intensity) radiation fields and instead uses a variable intensity pattern usually determined with a computerized optimization algorithm. This algorithm, often called 'inverse planning' is used to determine the intensity pattern to be delivered since there are too many individual 'beamlet' intensities involved to interactively determine the correct beamlet weights using forward planning by a dosimetrist. The combination of IMRT delivery with inverse planning tools is expected to achieve better dosimetric results than standard or 3-dimensional techniques, resulting in either the improvement of local control due to improved coverage of the target or reduced normal tissue dose while achieving the same tumor coverage.

Many techniques to intensity modulate dose in the treatment of breast cancer have been proposed and, in some cases, utilized in the clinic. The benefits of many of these techniques will be discussed.

With the advantages in dose homogeneity observed using IMRT for breast cancer, IMRT may appear to be the future 'gold standard' of radiotherapy. While this technical advance is truly promising, many

issues will have to be resolved before IMRT is routinely applicable. Adjustment for motion and daily set-up variation will be necessary to minimize rapid dose fall-off due to sharp dose gradients observed with IMRT. Improvements in dose homogeneity throughout the target and restriction of high dose to normal tissues may come at the expense of increased exposure of other tissues to low dose RT, the consequences of which are unknown. And finally, whether the dosimetric improvements obtained with IMRT will translate into improvement in clinical outcome is still unclear. These will be the challenges to be addressed in the next generation of clinical studies.

### MS3-1

#### Estrogen signaling from the plasma membrane in breast cancer.

Levin ER, *Long Beach VAMC, Long Beach, CA; UC-Irvine, Irvine, CA*

Rapid and more prolonged effects of estrogen result from steroid binding its receptor pools localized both in the plasma membrane and the nucleus. At the membrane of many target cells, estrogen binds classical ER $_{\alpha}$  and ER $_{\beta}$  receptors that are G-protein coupled in membrane rafts (such as caveolae). However, ER also may tether to the cytoplasmic face of the membrane via binding to caveolin-1. Caveolin-1 facilitates ER transport to the membrane through direct binding, and may serve as a scaffold to co-localize G proteins, growth factor receptor tyrosine kinases, and non-receptor tyrosine kinases (e.g. Src) at defined membrane areas. Co-localization with other signaling molecules facilitates rapid signaling by membrane ER and underlies the important effects of estrogen to promote growth and survival. In breast cancer, an important cross-talk occurs from membrane ER $_{\alpha}$  to transactivation of members of the EGF receptor family. The cross talk mainly requires the ligand binding domain of ER $_{\alpha}$  inducing the autophosphorylation of EGFR or ErbB2. The cross talk requires Src, matrix metalloproteinases II and IX, and the secretion of HB-EGF. EGFR autophosphorylation triggers cascades leading to the activation of ERK MAP kinase and PI3 kinase, cell cycle progression, and the survival of breast cancer cells. Specific targets of this signaling include the upregulation of cyclins D1 and B1 production, cell cycle kinase activation (Cdk4 and Cdc2), and transition through G1/S and G2/M checkpoints. Intact BRCA1 opposes many of these key functions of estrogen, a novel action for this tumor suppressor protein that is lost when BRCA1 is mutated in human breast cancer. Intact BRCA1 also prevents EGF and IGF-I signaling through ERK to proliferation. When the E domain of ER $_{\alpha}$  is targeted to the plasma membrane of ER negative breast cancer, E2 activation of ERK induces cell proliferation after 3-4 days of steroid exposure. This occurs despite the absence of the nuclear receptor. However, targeting the E domain to the nucleus also results in E2-induced proliferation, suggesting that both receptor pools are important. Intact BRCA1 inhibits proliferation in either model. Typical treatment for breast cancer includes taxol chemotherapy, radiation, or tamoxifen administration, and these modalities in part cause cancer cell apoptosis through inducing c-Jun N-terminal kinase upregulation, inactivating phosphorylation of Bcl-2 and Bcl $_{xL}$ , and inhibition of the apoptosome. Estrogen serves as a survival factor in these situations, and prevents the mentioned apoptotic signaling by transactivating EGFR and inhibiting JNK. Estrogen-induced survival also is linked to activation of ERK. Estrogen promotes the survival and migration of endothelial cells and enacts blood vessel formation via signaling through p38 MAP kinase; this is potentially relevant to tumor angiogenesis. Thus, rapid but sustained signaling from membrane estrogen receptors to the post-translational modification of existing proteins, and the transcriptional transactivation of target genes importantly contributes to breast cancer biology.

### MS3-2

#### ER interaction with AP-1.

Kushner PJ, *Metabolic Research Unit, San Francisco, CA*

Data Not Provided