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doi:10.1016/j.ijrobp.2006.07.1378

## CLINICAL INVESTIGATION

## Breast

## TARGETED INTRAOPERATIVE RADIOTHERAPY (TARGIT) YIELDS VERY LOW RECURRENCE RATES WHEN GIVEN AS A BOOST

JAYANT S. VAIDYA, M.B.B.S., M.S., D.N.B., F.R.C.S., PH.D., F.R.C.S. (GEN),\*

MICHAEL BAUM, M.B., F.R.C.S., C.H.M., M.D.(HON), F.R.C.R.(HON),<sup>†</sup>

JEFFREY S. TOBIAS, M.D., F.R.C.R.,<sup>†</sup> SAMUELE MASSARUT, M.D.,<sup>§</sup> FREDERIK WENZ, M.D.,<sup>‡</sup>

OLIVE MURPHY, B.Sc.,<sup>†</sup> BASIL HILARIS, M.D.,<sup>||</sup> JOAN HOUGHTON, B.Sc.,<sup>†</sup>

CHRISTOBEL SAUNDERS, M.D., F.R.C.S.,<sup>¶</sup> TAMMY CORICA, B.Sc.,<sup>¶</sup> MARIO RONCADIN, M.D.,<sup>§</sup>

UTA KRAUS-TIEFENBACHER, M.D.,<sup>‡</sup> FRANK MELCHAERT, M.D.,<sup>‡</sup> MOHAMMED KESHTGAR, F.R.C.S.,<sup>†</sup>

RICHARD SAINSBURY, F.R.C.S.,<sup>†</sup> MICHAEL DOUEK, F.R.C.S.,<sup>†</sup> ELLY HARRISON, B.Sc.,<sup>†</sup>

ALASTAIR THOMPSON, M.D., F.R.C.S.,\* AND DAVID JOSEPH, M.D.<sup>¶</sup>

\*Department of Surgery and Molecular Oncology, Ninewells Hospital and Medical School, University of Dundee, Dundee, United Kingdom; <sup>†</sup>Department of Surgery and Radiation Oncology, University College London, London, United Kingdom; <sup>‡</sup>Department of Surgery and Radiation Oncology, Centro di Riferimento Oncologico (CRO), Aviano, Italy; <sup>§</sup>Mannheim Medical Center, University of Mannheim, Mannheim, Germany; <sup>¶</sup>Department of Radiation Oncology, Sir Charles Gairdner Hospital and School of Surgery and Pathology, University of Western Australia, Perth, Australia; <sup>||</sup>Department of Radiation Oncology, Our Lady of Mercy, New York Medical College, New York, NY

**Purpose:** Patients undergoing breast-conserving surgery were offered boost radiotherapy with targeted intraoperative radiotherapy (TARGIT) using the Intrabeam system to test the feasibility, safety, and efficacy of the new approach.

**Methods and Materials:** We treated 302 cancers in 301 unselected patients. This was *not* a low-risk group. One-third of patients (98/301) were younger than 51 years of age. More than half of the tumors (172, 57%) were between 1 cm and 2 cm, and one-fifth (62, 21%) were >2 cm; 29% (86) had a Grade 3 tumor and, in 29% (87), axillary lymph nodes contained metastasis. After primary surgery, 20 Gy was delivered intraoperatively to the surface of the tumor bed, followed by external-beam radiotherapy (EBRT), but excluding the usual boost.

**Results:** The treatment was well tolerated. The follow-up ranged from 3 to 80 months (164 and 90 patients completed 2 and 3 years follow-up, respectively). Four patients (1.3%) had local recurrence. The Kaplan-Meier estimate of local recurrence is 2.6% (SE = 1.7) at 5 years. This compares favorably with the 4.3% recurrence rate in boosted patients from the EORTC boost study, in which only 8.1% patients were node-positive, as opposed to 29% in our series.

**Conclusion:** Targeted intraoperative radiotherapy combined with EBRT results in a low local recurrence rate. This could be attributed to both accurate targeting and timeliness of the treatment. These data support the need for a randomized trial to test whether the TARGIT boost is superior to conventional external boost, especially in high-risk women. © 2006 Elsevier Inc.

**Breast cancer, Targeted intraoperative radiotherapy (TARGIT), Boost, Recurrence rate, Breast-conserving surgery.**

### INTRODUCTION

Early local recurrences after breast-conserving surgery and postoperative radiotherapy for breast cancer most com-

monly occur in the vicinity of the primary tumor bed (1). A radiotherapy boost to the tumor bed is therefore part of standard treatment. However, accurate targeting of this boost can be difficult because of deformation and positional

Reprint requests to: Jayant S. Vaidya, M.B.B.S., M.S., D.N.B., F.R.C.S., Ph.D., F.R.C.S. (GEN), Surgery and Molecular Oncology, Level 6, Ninewells Hospital and Medical School, University of Dundee, DD12UY, Dundee, Scotland, United Kingdom. Tel: (+44) 138-266-0111; Fax: (+44) 138-249-6363; E-mail: j.s.vaidya@dundee.ac.uk

J.S.V., M.B., and J.S.T. conceived the study.

J.S.V., M.B., J.S.T., S.M., M.R., B.H., U.K., F.W., D.J., C.S., A.M.T., J.A.D. recruited and treated patients. J.S.V., M.B., J.S.T.,

S.M., M.R., B.H., U.K., F.W., D.J., C.S., A.M.T., J.A.D., E.H., and J.H. collected the data.

M.K., R.S., M.D., and F.M. were involved in later follow-up care.

J.S.V., O.M., S.M., U.K.T., T.C., and B.H. analyzed the data.

J.S.V. and S.M. wrote the first draft and all other authors contributed to the final manuscript.

Received May 11, 2006, and in revised form July 21, 2006.

Accepted for publication July 27, 2006.

change of the postoperative breast, particularly because there is often a considerable delay between surgery and radiotherapy planning. A “geographical miss” occurs in 50–80% of patients (2–4) and this may contribute toward a proportion of local recurrences. Modern radiotherapy planning by computed tomography simulation, in which surgical clips are outlined, may be able to reduce this. However, a much simpler and direct method may be to use intraoperative radiotherapy.

We developed a novel technique of delivering intraoperative therapeutic irradiation that we call *targeted intraoperative radiotherapy* (TARGIT) (5, 6). With this technique, using the Intrabeam system, the target tissue—namely, the tumor bed—is wrapped around or conformed to the radiotherapy source, which delivers radiotherapy from within the breast, usually under the same anesthetic as the primary surgery. The procedure can be performed in a standard operating theater and adds 20 to 40 min to the operation time.

We are currently testing whether partial-breast irradiation, using this technique in selected patients, can replace conventional whole-breast external-beam radiotherapy (EBRT) in a multicenter randomized trial (7, 8). Centers participating in this trial initially treated a series of pilot cases to test the feasibility and safety of using the new technique of intraoperative radiotherapy supplemented by standard EBRT in patients with a high risk of local recurrence. This article describes the outcomes in relation to local recurrence, among the 301 consecutive patients in whom intraoperative radiotherapy was used as a tumor bed boost.

## METHODS AND MATERIALS

The study protocol was approved by the local ethics committee in each center. Patients of any age suitable for breast-conserving surgery were approached and consented to participate in the pilot studies at each of the five centers. Tumors were unifocal on mammography up to 4 cm in diameter. There was no restriction by tumor type, tumor grade, receptor status, or axillary lymph node involvement. Each patient had her breast-conserving surgery as per local protocol—typically a wide local excision of the primary tumor and axillary surgery. Patients with incompletely excised positive margins or positive margins who had a re-excision or mastectomy (which effectively excised the tissues that were irradiated during intraoperative radiotherapy) were excluded from further analysis.

Intraoperative radiotherapy using the Intrabeam system was delivered to the tumor bed immediately after surgical excision during the same anesthesia, as previously described (6). In 9 patients in the Australian cohort, intraoperative radiotherapy was delivered as a second operation within a few weeks (median 4.9 weeks) for logistical reasons. The radiation dose received by the tumor bed was between 18–20 Gy at the surface of the applicator and 5–7 Gy at 1 cm into the surrounding tissues. In the U.K., American, Australian, and Italian patients, the dose prescription was 5 Gy at 1 cm, effectively delivering 18–20 Gy to the applicator surface depending on the size of the applicator. In Germany, because of local regulations, the dose was prescribed as 20 Gy, which effectively delivered between 5–7 Gy at 1 cm, again depending on the

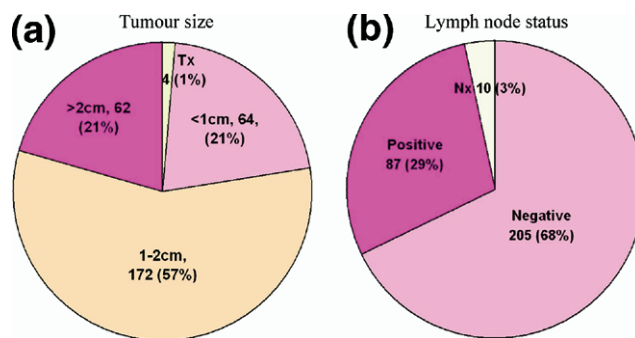


Fig. 1. Pathological tumor size and nodal status.

size of the applicator. The additional time required for setup and delivery of intraoperative radiotherapy was between 30–50 min, depending on the size of the applicator. After completion of radiotherapy and wound closure, patients were discharged home according to local practice.

All patients received the planned EBRT (typically 45–50 Gy in 25 fractions over 5 weeks) to the whole breast, delivered as per local protocol. If adjuvant chemotherapy was given, EBRT followed. Patients were followed up with at least a 6-monthly clinical examination and an annual mammogram.

## RESULTS

Between July 1998 and Aug 2005, 321 patients participated in this pilot study; 20 patients were excluded. One patient had multiple diffuse margin involvement and declined further surgery, 1 patient had bilateral prophylactic mastectomy (at her request), and 18 patients had further surgery for involved margins: 13 mastectomy and 5 re-excision. Thus, the total evaluable patients included in this study are 301. One patient had bilateral cancers treated, making the total number of cancers equal to 302. Seven patients with focally positive margins who did not have a re-excision were *not* excluded.

The median age was 57 years (range, 28–83 years). One-third (98/301) were younger than 51 years. Only 21% of tumors (64) were <1 cm in size. More than half of the tumors (172, 57%) were between 1–2 cm; 21% (62) were >2 cm (Fig. 1a); 22% (68) tumors were Grade 1; 49% (148) were Grade 2; and 29% (86) were Grade 3. Eighty-seven patients (29%) patients had involved axillary lymph nodes (Fig. 1b).

The range of follow-up is 3 to 80 months and reflects the staggered starting of the study at the five centers. One hundred sixty-four patients have completed 2-year follow-up, 90 patients have completed 3-year, and 28 patients have completed 5-year follow-up.

Figure 2 gives a Kaplan-Meier plot of recurrences. The 5-year actuarial recurrence rate is 2.6% (SE = 1.7). Four patients had ipsilateral breast tumor recurrence at 10, 32, 40, and 77 months' follow-up and Table 1 gives the details. None of the patients who had focally involved margins and were not re-excised had a recurrence. Five patients (1.7%) died from nonbreast cancer causes. Two of these were from

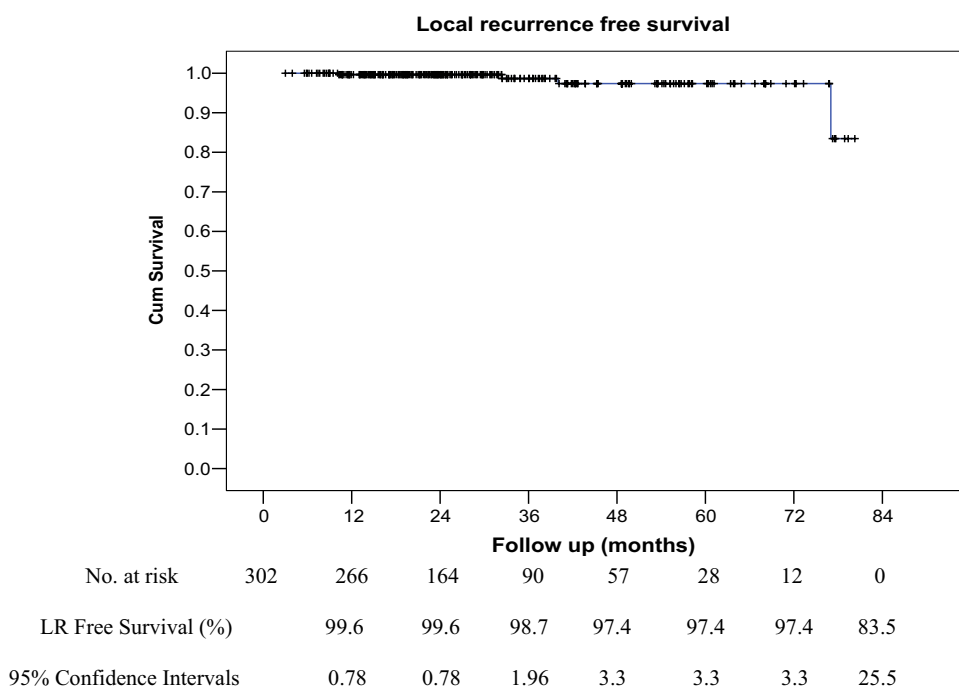


Fig. 2. Kaplan-Meier plot of local recurrence (LR) free survival.

lung cancer at the ages of 57 and 70 years, two were from heart disease at 70 and 79 years, and one died of indeterminate cause. Five patients (1.7%) died from metastatic breast cancer. The sites of metastasis were the pleura, brain, lung, liver, and liver plus brain.

## DISCUSSION

This study demonstrates that radiotherapy targeted to the tumor bed, when it is most accessible at the time of surgery for the cancer, is associated with a low rate of local disease recurrence: 2.6% in actuarial terms at 5 years. The patient population in this series is representative of patients suitable for breast-conserving therapy (with T1 = 78% and T2 =

21%, Gr1 = 22%, Gr2 = 48.8%, Gr3 = 28.7%, and 29% node-positive). Approximately one-third (98/301) of these patients were younger than 51 years, and 7 patients had focally involved margins but did not have further surgery.

Furthermore, of the 4 patients with recurrences, two were second primary lesions in a separate quadrant irradiated as part of whole-breast EBRT and one was a multifocal diffuse recurrence, leaving one that could be interpreted as a “true” tumor bed recurrence among 301 patients, a focus of ductal carcinoma *in situ*.

Acute toxicity was rare and has been previously documented for the German (9), Australian (10), and U.K. cohorts (5, 11). Of note, there was no problem with wound healing, even in patients who needed to have subsequent

Table 1. Accrual and recurrences at individual centers.

	Accrual	No. of cancers	Recurrences
United Kingdom	July 1998 (1) Sept 1998 (1) March 1999–March 2000 (20) Nov–Dec 2004 (2)	24	2 cases: Both new primary lesions outside the index quadrant at 40 m and 77 m
United States	May 2000 to Dec 2002	50	1 case: A focus of DCIS in the scar at 32 mo
Australia	Aug 2001 to Oct 2003 (No accrual between Dec 2001–March 2002 and July–Nov 2002)	31	0 cases
Germany	Feb 2002–Aug 2005	85	1 case: Diffuse recurrence including skin at 10 mo—died soon after
Italy	Sept 2002–Dec 2004	112	0 cases
Total		302	4 cases (1.3%)

Abbreviation: DCIS = ductal carcinoma *in situ*.

surgery in the form of re-excision or mastectomy for diffusely positive margins. The cosmetic outcome of a small subset of these patients has been analyzed and was found to be satisfactory (12).

Compared with other methods of partial-breast irradiation, the combination of TARGIT with EBRT is feasible, providing a well-targeted boost dose that may not be achieved even with the most sophisticated 3D planning. Furthermore, it does not require any additional sessions. It ensures excellent conformation and dosimetry and reduces the risk of a “geographical miss,” justifying the term *intraoperative conformal brachytherapy* (13).

We believe that the low early local recurrence rate in the present series has been achieved because of outstandingly accurate and timely targeting of the tumor bed. This may be related both to the proximity of the radiation source but also to the timing of radiotherapy immediately after surgery, when the wound (tumor bed) may otherwise form a fertile milieu for cancer cells (14). This latter may outweigh any theoretical disadvantages of “splitting” the radiotherapy course. A mathematical model comparing radiotherapy strategies (15) (TARGIT vs. EBRT) has suggested that TARGIT may achieve better local control. The single high dose delivered to the tissues immediately surrounding the tumor may eliminate not only residual cancer cells, but also putative cancer cells (which harbor loss of heterozygosity

and other precancerous genetic changes) but are sufficiently “normal” so that they remain protected during conventional radiotherapy because of its low-dose fractions.

The estimated 5-year recurrence rate of 2.6% that has been achieved in this series compares well with the recurrence rate of 4.3% in the EORTC study (16). In the EORTC study, it was found that the boost mainly has benefit under the age of 51. In this age group, our series had a recurrence rate of 3.85% compared with 6.9% in the EORTC study (16). The low recurrence rate in our series was achieved despite having poorer prognosis tumors: 29% of patients in our series had lymph node metastasis, compared with only 8.1% of patients in the EORTC study (16).

We realize that, although 90 patients have been followed up for more than 3 years, less than 10% of cases were followed up for more than 5 years and, with further follow-up, the recurrence rate may rise above 2.6%. However, we are encouraged by the 95% confidence limits of the estimated 5-year actuarial local recurrence rate (0–5.9%) that do not reach a high level in this relatively high-risk population.

The time is ripe for a randomized trial to test whether the conventional external boost should be replaced by TARGIT, especially in high-risk women. We are planning to commence this superiority study—TARGIT-B (Boost)—to run in parallel with the ongoing TARGIT-A (Alone) equivalence trial.

## REFERENCES

- Vaidya JS, Vyas JJ, Mitra I, *et al*. Multicentricity and its influence on conservative breast cancer treatment strategy. *Hong Kong Int Cancer Congress* 1995 November; Abstract 44.4.
- Machtay M, Lanciano R, Hoffman J, *et al*. Inaccuracies in using the lumpectomy scar for planning electron boosts in primary breast carcinoma. *Int J Radiat Oncol Biol Phys* 1994; 30:43–48.
- Sedlmayer F, Rahim HB, Kogelnik HD, *et al*. Quality assurance in breast cancer brachytherapy: Geographic miss in the interstitial boost treatment of the tumor bed. *Int J Radiat Oncol Biol Phys* 1996;34:1133–1139.
- Benda RK, Yasuda G, Sethi A, *et al*. Breast boost: Are we missing the target? *Cancer* 2003;97:905–909.
- Vaidya JS, Baum M, Tobias JS, *et al*. Targeted intraoperative radiotherapy (TARGIT): An innovative method of treatment for early breast cancer. *Ann Oncol* 2001;12:1075–1080.
- Vaidya JS, Baum M, Tobias JS, *et al*. The novel technique of delivering targeted intraoperative radiotherapy (TARGIT) for early breast cancer. *Eur J Surg Oncol* 2002;28:447–454.
- Vaidya JS, Baum M, Tobias JS, *et al*. Targeted Intraoperative Radiotherapy (TARGIT)—trial protocol. *Lancet* online, 1999. Available at: <http://www.thelancet.com/journals/lancet/misc/protocol/99PRT-47>.
- Vaidya JS, Joseph D, Hilaris BS, *et al*. Targeted intraoperative radiotherapy for breast cancer: An international trial. *Abstract Book of ESTRO-21 (Prague)* 2002;21:135.
- Kraus-Tiefenbacher U, Scheda A, Steil V, *et al*. Intraoperative radiotherapy (IORT) for breast cancer using the Intrabeam system. *Tumori* 2005;91:339–345.
- Joseph DJ, Bydder S, Jackson LR, *et al*. Prospective trial of intraoperative radiation treatment for breast cancer. *ANZ J Surg* 2004;74:1043–1048.
- Vaidya JS. A novel approach for local treatment of early breast cancer. PhD thesis, University of London, May 2002;1–242.
- Vaidya JS, Wilson AJ, Houghton J, *et al*. Cosmetic outcome after targeted intraoperative radiotherapy (TARGIT) for early breast cancer. *Breast Cancer Res Treatment* 2003;82:1039.
- Tobias JS, Vaidya JS, Keshtgar M, *et al*. Reducing radiotherapy dose in early breast cancer: The concept of conformal intraoperative brachytherapy. *Br J Radiol* 2004;77:279–284.
- Massarut S, Baldassarre G, Belletti B, *et al*. Intraoperative radiotherapy impairs breast cancer cell motility by surgical wound fluid [Abstract]. *J Clin Oncol* 2006;24(18 suppl.): 10611.
- Enderling H, Anderson AR, Chaplain MA, *et al*. Mathematical modelling of radiotherapy strategies for early breast cancer. *J Theor Biol* 2006;241:158–171.
- Bartelink H, Horiot JC, Poortmans P, *et al*. Recurrence rates after treatment of breast cancer with standard radiotherapy with or without additional radiation. *N Engl J Med* 2001;345: 1378–1387.