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CLINICAL INVESTIGATION

LONG-TERM RESULTS OF TARGETED INTRAOPERATIVE RADIOTHERAPY (TARGIT) BOOST DURING BREAST-CONSERVING SURGERY

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Purpose: **We have previously shown that delivering targeted radiotherapy to the tumour bed intraoperatively is feasible and desirable. In this study, we report on the feasibility, safety, and long-term efficacy of TARGeted Intraoperative radioTherapy (Targit), using the Intrabeam system.**

Methods and Materials: **A total of 300 cancers in 299 unselected patients underwent breast-conserving surgery and Targit as a boost to the tumor bed. After lumpectomy, a single dose of 20 Gy was delivered intraoperatively. Postoperative external beam whole-breast radiotherapy excluded the usual boost. We also performed a novel individualized case control (ICC) analysis that computed the expected recurrences for the cohort by estimating the risk of recurrence for each patient using their characteristics and follow-up period.**

Results: **The treatment was well tolerated. The median follow up was 60.5 months (range, 10–122 months). Eight patients have had ipsilateral recurrence: 5-year Kaplan Meier estimate for ipsilateral recurrence is 1.73% (SE 0.77), which compares well with that seen in the boosted patients in the European Organization for Research and Treatment of Cancer study (4.3%) and the UK STAndardisation of breast RadioTherapy study (2.8%). In a novel ICC analysis of 242 of the patients, we estimated that there should be 11.4 recurrences; in this group, only 6 recurrences were observed.**

Conclusions: **Lumpectomy and Targit boost combined with external beam radiotherapy results in a low local recurrence rate in a standard risk patient population. Accurate localization and the immediacy of the treatment that has a favorable effect on tumour microenvironment may contribute to this effect. These long-term data establish the long-term safety and efficacy of the Targit technique and generate the hypothesis that Targit boost might be superior to an external beam boost in its efficacy and justifies a randomized trial.** **© 2010 Elsevier Inc.**

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

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The study protocol was approved by the local ethics committee in each centre.

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INTRODUCTION

The addition of a tumor bed boost to the course of whole-breast radiotherapy further reduces the local recurrence and the proportional reduction is not age-dependent (1). This is not surprising as early local recurrences after breast-conserving surgery most commonly occur in the vicinity of the primary tumor bed (2–4). It seems logical that it is this area that needs most intensive treatment, though many problems remain, which are difficult to solve by using conventional external beam radiotherapy. First, the accurate targeting of this boost can be difficult because of deformation and positional change of the postoperative breast that is further complicated in cases undergoing "onco-plastic" surgery when the position of the "tumor bed" is virtually impossible to predict. Second, there is often a considerable delay between surgery and radiotherapy planning. Not only can this delay contribute to a "geographical miss" that has been shown to occur in at least half (50–80%) of patients (5–7), but it may also cause a biologically relevant delay that we call a *temporal miss* (8). Modern radiotherapy planning by computed tomography simulation in which surgical clips are outlined on the simulator may be able to reduce but cannot eliminate a geographical miss. However, a much simpler and direct method may be to use targeted intraoperative radiotherapy to deliver immediate irradiation to the tumor bed.

Over the last 13 years, we have developed an innovative technique to deliver intraoperative therapeutic irradiation that we call targeted intraoperative radiotherapy (Targit) (9–11). 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 theatre and adds 20–40 min to the operation time.

In the international Targit-A trial, a randomized controlled trial, we are testing whether targeted intraoperative radiotherapy, in selected patients, can replace conventional whole breast external beam radiotherapy (12–14). The initial centers while planning to participate in this trial treated a series of pilot cases to test the feasibility and safety of using the Targit technique as a substitute for the usual tumor bed boost in a series of 299 unselected patients undergoing breast-conserving therapy. We have previously reported that the local recurrence in this group, with a relatively short follow up was low (5-year actuarial 2.6% SE 1.7) (15). However the upper limit of the confidence interval was 5.9%. We presented an update (16) at the ASCO (American Society of Clinical Oncology) meeting in 2008 (5-year actuarial recurrence rate 1.52%; SE 0.76). In this article, we update these results at a maximum follow up of 122 months and a median follow-up of 60.5 months (~5 years).

MATERIALS AND METHODS

The method has been described previously (9–11) http://www.targit.org.uk. The study protocol was approved by the local ethics committee in each center. Consecutive patients of any age at each center, diagnosed with invasive breast cancer and found suitable for breast-conserving surgery, were approached and informed consent was obtained. Each of the tumors in this study was unifocal on mammography and none was >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 reexcision 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 anaesthesia, as previously described (10, 15). 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 Gy to 20 Gy at the surface of the applicator, and 5–7 Gy at 1 cm into the surrounding tissues. The additional time required for setup and delivery of intraoperative radiotherapy was between 30 and 50 min, depending on the size of the applicator. After completion of radiotherapy and wound closure, patients were discharged home according to local practice (15).

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

Statistical analysis was performed using the SPSS package (SPSS for Windows, Rel. 14.0.1. 2005. Chicago: SPSS Inc. 14). Kaplan-Meier survival analysis plots were created.

We compared our results with those obtained in two large contemporary clinical trials (European Organization for Research and Treatment of Cancer [EORTC] and UK STAndardisation of breast RadioTherapy [START-B] trials) (17–19) in which the patients were treated in centers of excellence with the best possible care.

We also performed a novel analysis. Briefly, we used a contemporary model of prediction of local recurrence with current therapy (www.nemc.org/ibtr, which has been recently validated) (20) to estimate the risk of local recurrence in each of the 242 patients in whom all the necessary data required for the model were available. To do this, we input each patient's and tumor characteristics and the length of the individual follow-up into the model. We thus created a virtual set of controls modelled to not just age, but for all the exact patient characteristics matched for each patient. The mathematical model therefore estimated the risk of local recurrence for this model cohort, which was matched to the exact patient characteristics in the study group. We then compared this estimated number of recurrences with the observed numbers. We call this new method "individual case-control analysis" (Table 1A).

RESULTS

Between July 2, 1998, and August 11, 2005, 319 patients with invasive breast carcinoma participated in this study. Twenty patients were excluded from further analysis: 1 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

Table 1. Individualized case control (ICC) analysis

Column 1	Column 2	Column 3	Column 4	Column 5	Column n	
Prognostic Factor	Coefficients	Patient A	Patient B	Patient C	Patient N	Results Column
Age	a	a x (age of A)	a x (age of B)	…	a x (age of N)	
pT	t	t x (pT of A)	t x (pT of B)	…	t x (pT of N)	
Grade	g	g x (Gr of A)	g x (Gr of B)	…	g x (Gr of N)	
Margins	m	m x (M of A)	m x (M of B)	…	m x (M of N)	
Lymphovascular invasion	l	l x (LVI of A)	l x (LVI of B)	…	l x (LVI of N)	
Chemotherapy	c	c x (chemo given or not to A)	c x (chemo given or not to B)	…	c x (chemo given or not to N)	
Hormone therapy	h	h x (hormones given or not to A)	h x (hormones given or not to B)	…	h x (hormones given or not to N)	
10-year risk of recurrence		Standard risk of A at 10 years	Standard risk of B at 10 years	…	Standard risk of N at 10 years	
Individualized risk of recurrence	As per actual follow-up and nodes*	Individualized risk of recurrence of A for actual follow-up of A	Individualized risk of recurrence of B for actual follow-up of B		Individualized risk of recurrence of N for actual follow up of N	Total risk of the cohort and expected number of recurrences, which in our study was 11.4

The prognostic factors for local recurrence at 10 years and their coefficients (columns 1 and 2) are taken from http://www.nemc.org/ibtr. These coefficients are then applied to each patient's individual characteristics in columns 3, 4, 5, … n. The penultimate row calculates the 10-year risk of recurrence for each patient.

* The last row calculates the risk of each patient including the fact that of the recurrences that occur the first 10 years, 83% occur in the first 5 years for node-positive women and 67% occur in the first 5 years for node-negative women (22).

involved margins: 13 had a mastectomy and 5 had reexcision. Thus the total evaluable patients included in this study are 299. One patient had bilateral cancers treated, so the total number of cancers is 300. Seven patients with focally positive margins who did not have a reexcision were not excluded. In our first article (21), we reported on 321 patients; however, it was later discovered that 2 of these patients did not actually take external beam radiotherapy; 1 refused and the other had received mantle radiotherapy for Hodgkin disease in the past. Hence these patients are not considered in this article.

Table 2A. Patient and tumor characteristics

Age	
≤40	21
41–45	24
46–50	50
51–55	34
56–60	45
61–65	44
66–70	40
71–75	27
>75	14
Pathologic tumor size	
<1 cm	63
1–2 cm	172
2.1– 3 cm	52
>3 cm	9
Unknown	4
Tumor grade	
1	67
2	146
3	86
Unknown	1
Lymph nodes	
Negative	204
Positive	87
Unknown	9

In terms of the tumor characteristics of the patients in our trial, it was clearly not a selected good-prognosis cohort (Table 2A). The median age was 57 years (range, 28–83 years). A third (96/299) was younger than 51 years. Only 21% of tumors (n = 63) were <1 cm in size; more than half the tumors (172, 58%) were 1–2 cm, 20% (n = 61) were larger than 2 cm (Figure 1A); 22% (n = 67) tumors were Grade 1, 49% (n = 147) were Grade 2, and 29% (n = 86) were Grade 3; 29.9% (n = 87) patients had involved axillary lymph nodes. Of the 242 patients in whom the systemic treatment was analyzed, 39% (n = 94) received chemotherapy and 81% (n = 195) received hormone therapy.

The first patient was treated in July 1998 and is alive and well at a follow-up of 10 years. The median follow-up is 60.5 months (range, 10–122 months). Eight patients have had ipsilateral breast tumor recurrence: 5-year Kaplan Meier estimate for ipsilateral recurrence is 1.73% (SE 0.77) (Figure 1). Five of these 8 patients had recurrence in the tumor bed: 5-year Kaplan Meier tumor bed recurrence rate was 1.04% (SE 0.59). The 5-year Kaplan-Meier recurrence rate in women younger than age 50 was 2.1% (SE 1.5), compared with 6.9% in the EORTC study (19). Additionally, 7 patients developed contralateral breast cancer.

Two major trials of radiotherapy boost allow us to have a benchmark for our study: the EORTC study (1) and the

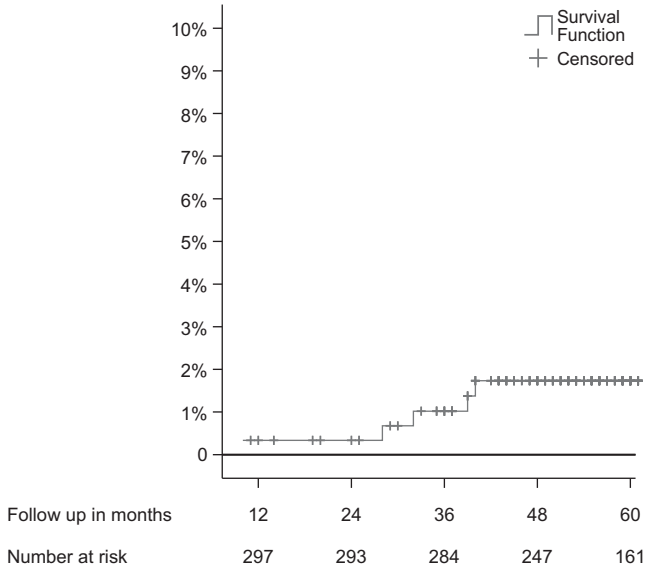

Fig. 1. Kaplan-Meier Plot for local recurrence in the 300 breast cancers treated with lumpectomy, tumor bed boost with targeted intraoperative radiotherapy, and whole-breast radiotherapy. Ipsilateral local recurrences occurred at 10, 28, 32, 39, 40, 62, 69 and 77 months. The median follow-up is 60.5 months and the 5-year actuarial recurrence rate is 1.73% (SE 0.77).

START-B study (18). The EORTC study reported a 5-year recurrence in boosted patients of 4.3% and the START-B 2.8%. The 5-year recurrence in the TARGIT group was 1.73%; it is important to note that patients in our study had a higher node positivity (29.9%) compared with 21% in the EORTC and 24% in START-B trial (Table 2B). However, the number of patients in this Phase II study is small and any semblance of superiority may have arisen by chance. Nevertheless, we feel that these data, as well as the results from the translational work are enough to justify a randomized trial to test whether there is any additional benefit of giving the tumor bed boost intraoperatively.

This plausibility of superior local control is supported by results of our novel individual case-control analysis (Table 1). A total of 242 patients in the study had all the parameters available for this analysis. We found that the mathematical model using individual patient (*i.e.*, case-control) estimated that the 10-year risk of local recurrence should be 7.8%. In the Early Breast Cancer Trialists' Collaborative Group overview, local recurrences occurred in the first 5 years in 67% of node-negative patients and 83% in node-positive patients. Adding this to the model for each patient, including individual follow-up, we should expect that 4.7% (*i.e.*, 11.4 patients) should have recurred at current follow-up. In reality here were only six recurrences–nearly half of the expected from the model. We should interpret this finding with caution; first, because it could have arisen by chance and second, it is after all only a model and only data from a randomized study will provide reliable evidence.

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

High-risk factors	EORTC boost	START-B trial	Targit boost
Young age	33% were ≤50	21% were <50	32% were ≤50
% >1 cm	75%	86%	78%
% Grade 3	Not available	23%	29%
% Node +	21%	23.6%	29%
Recurrence rate at 5 years	4.3%	2.8%	1.73%

Abbreviations: EORTC = european organization for research and treatment of cancer; START-B = standardisation of breast radiotherapy study.

DISCUSSION

The 5-year recurrence rate of 1.73% that has been achieved in this mature series compares well with the recurrence rate of 4.3% in the EORTC study (17, 19), despite having poorer prognosis tumors. Considering the location of the recurrence in the breast, five of the eight local recurrences were in the tumor bed, which could be interpreted as "true" recurrences and the Kaplan-Meier estimate for such recurrence is only 1.04% at 5 years (SE 0.59) (*i.e.*, ∼0.2% per year). The individualized case control analysis suggests that the number of recurrences in this cohort are about half of the expected number of recurrence. We again urge caution in overinterpreting this analysis that uses the nemc.org model because it is in its early stages of being validated. Finally, in the EORTC study, it was found that the absolute benefit of the boost was larger in women younger than age 51 compared with older women, being the largest in those under 40. Four of the eight recurrences in our series occurred in women younger than 50, and the 5-year Kaplan-Meier recurrence rate was 2.1% (SE 1.5) compared with 6.9% in the EORTC study (17, 19). Again the numbers are small and this finding should only be considered as hypothesis generating.

Postoperative radiotherapy reduces the risk of local recurrence after breast-conserving surgery by approximately two thirds (22). Although it is presumed that radiotherapy works by eradicating residual tumor cells after surgery, this thesis needs careful examination.

First, a long-standing and biologically interesting puzzle is that this proportional risk reduction is the same whether the margins are positive, narrow or wide. For example, in the EORTC study (23), there was no formal assessment of margins and many could have been positive; in the NSABP (National Surgical Adjuvant Breast and Bowel Project) study (24), the margins were narrow (lumpectomy), whereas in the two Milan studies (25–27), the margins were either narrow (lumpectomy) or very wide (quadrantectomy). Finally, the margins are generally the widest after a mastectomy (22). However, in all these situations, the proportional reduction in recurrence rate in all these studies is very similar (about two thirds). Furthermore, in a recent report from the EORTC, study margin status was not found to influence recurrence rate (28). In a modern surgical oncology practice, margin status is meticulously assessed and a negative margin is achieved at the end of surgical treatment

in most cases. If after this, none or very few tumor cells are left behind, and radiotherapy still makes a difference, then what is the radiotherapy treating?

We hypothesize that radiotherapy has a significant effect on the tumor microenvironment–the tumor bed–where most recurrence occurs and have subsequently found translational research evidence (29–32) to support our ideas. Wound fluid that collects in the tumor bed after a lumpectomy provides an excellent medium for any remaining or circulating tumor cells. Compared with preoperative serum, the wound fluid collected in the first 24 h from a normal lumpectomy cavity stimulates proliferation, motility, and invasion; on the other hand, when the fluid from patients who have received targeted intraoperative radiotherapy is tested, this effect is abrogated (30–32). This abrogation of postsurgical response by intraoperative radiotherapy may be even more important in younger women who may have had a relative evolutionary advantage of having a growth-promoting effect in their wound fluids. Moreover, even if no pathologically detectable tumor cells remain after surgery, it is likely that genetic or epigenetic changes in surrounding tissues may influence recurrence (33, 34) and that remaining tumor cells may have undergone mesenchyme transition thus entered dormancy (35). Circulating tumor cells have been demonstrated to have the ability to go back to the primary tumor site and boost its growth (36); thus, it is plausible that such circulating tumor cells could also be attracted to the surgical wound. The normal surgical wound fluid may therefore provide an ideal microenvironment for tumor cell growth and it follows that the temporal proximity of radiotherapy to surgical wounding may be of considerable importance to its effectiveness.

Giving the single well-targeted dose of radiotherapy to the tumor bed at the time of surgery inevitably "splits" the "conventional" schedule of radiotherapy and this does not accord with the conventional modeling of radiotherapy. In fact, in 45% of patients in this study, chemotherapy was given after surgery and intraoperative radiotherapy, and before the usual course of fractionated radiotherapy, without jeopardizing the effectiveness. This single dose should not be considered as just another fraction in the course of conventional radiotherapy schedule, because it is inherently different in several aspects. It may be that despite this "splitting," or rather because of its lending temporal proximity to surgery that cannot ever be achieved by conventional radiotherapy, that a low recurrence rate was achieved by Targit.

Second, the single high dose delivered to the tissues immediately surrounding the tumor may also eliminate morphologically normal putative cancer cells that harbor loss of heterozygosity and other precancerous genetic changes (33, 37) but are sufficiently "normal" so that they remain protected during conventional radiotherapy because of its low-dose fractions. A mathematical model comparing radiotherapy strategies (38, 39) (Targit vs. external beam radiotherapy) suggests that the Targit approach may achieve better local control. The results of this mathematical model correlates well with the recent results of the START trials (18, 40) which suggest that breast tissue may be more sensitive to fraction size than previously thought and that a smaller number of relatively larger fractions may be the better option, although in an exploratory subgroup analysis of the Canadian study of hypofractionation, it appeared to be less effective for high-grade tumors than for lower grade tumors (41).

Finally, the implication of a two-thirds risk reduction by conventional radiotherapy is that radiotherapy fails in a third of cases. This translates into a significant absolute number of recurrences in women with high risk of local recurrence. It is in these, mainly young women, that an improvement in local control would have the greatest impact and a TARGIT-Boost may potentially achieve this goal.

This study demonstrates with a mature follow-up that radiotherapy targeted to the tumor bed when it is most accessible at the time of surgery, is associated with a rate of local disease recurrence that is lower than would have been expected for this standard risk population of patients.

It could be argued that the contralateral breast is considered as an internal control. With that perspective, we found that the appearance of a cancer during the prolonged follow-up on either side is not too different (eight vs. seven) suggesting that the combined treatment of the diseased breast rendered it equivalent to the "normal" contralateral breast.

Acute toxicity was rare and has been previously documented for the German (42), Australian (14), and the UK cohorts (11, 43). Of note, there was no problem with wound healing even in those patients who needed to have subsequent surgery in the form of reexcision or mastectomy for diffusely positive margins. The cosmetic outcome of a small subset of these patients has also been analyzed and was found to be satisfactory (42, 44–46) and comprehensive cosmetic analysis will be the subject of another article. We wish to emphasize that although the surface dose is 20 Gy, it is attenuated very quickly to 5–7 Gy at 1 cm so the volume of breast tissue that receives a high dose is much lower than would be expected from a homogenous dose distribution. We are indeed mindful of radiation toxicity such as fibrosis, which can appear after many years and are monitoring our cohort for this.

Compared with other methods of partial breast irradiation, the combination of targeted intraoperative radiotherapy with external beam radiotherapy is feasible and provides a well timed and targeted boost dose that may not be achieved even with the most sophisticated three-dimensional planning. Furthermore, it saves a few (five to eight) sessions and patient visits to the radiotherapy department. It ensures excellent conformation and dosimetry and reduces the risk of both a "geographical miss" and a "temporal miss." Our results are in concordance with the report from the Milan group that also used intraoperative radiotherapy as a boost (47) and found acceptable rates of toxicity.

Giving Targit as the only treatment for relatively low-risk patients was tested in the Targit-A trial. This international prospective randomized controlled Phase III trial recruited patients from 28 centers and compared the policy of targeted intraoperative radiotherapy as the sole radiation treatment

with conventional whole-breast external beam radiotherapy after breast-conserving surgery. The results (48) (Lancet Online First, doi:10.1016/S0140-6736(10)60837-9) indicated that single-dose Targit yields local recurrence rate noninferior to whole-breast external beam radiotherapy along with lower radiotherapy toxicity. The difference in local recurrence in the conserved breast, between the Targit group and the conventional whole -breast external beam radiotherapy group at 4 years was not statistically significant: 0.25% (95% CI -1.0% to +1.5%).

Giving TARGIT as the boost dose is already being used in several centers around the world and is included in several national guidelines as an option. This study gives new evidence of long-term safety and efficacy. It also generates the hypothesis that a Targit boost might be superior to conventional external beam boost. Hence we have launched a randomized clinical trial to test this hypothesis (Targit-Boost trial) in high-risk women aiming ultimately, for an approach of risk-adapted radiotherapy, viz. TARGIT-Alone for low risk and TARGIT-Boost for high risk patients.

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