Intraoperative Radiation Therapy: A Critical Analysis of the ELIOT and TARGIT Trials. Part 2—TARGIT

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ABSTRACT

Background. Two randomized intraoperative radiation therapy trials for early-stage breast cancer were recently published. The ELIOT Trial used electrons (IOERT), and the TARGIT-A Trial Update used 50-kV X-rays (IORT). These studies were compared for similarities and differences. The results were analyzed and used to determine which patients might be suitable for single-dose treatment.

Methods. The primary sources of data were the ELIOT Trial and TARGIT-A Trial, as well as a comprehensive analysis of the peer-reviewed literature of accelerated partial breast irradiation (APBI) using 50-kV X-rays or electrons. Studies published or presented prior to March 2014 were analyzed for efficacy, patient restrictions, complications, and outcome.

Results. With a median follow-up of 5.8 years, the 5-year recurrence rates for ELIOT versus EBRT patients were 4.4 and 0.4 %, respectively, \( p = 0.0001 \). A low-risk ELIOT group was identified with a 5-year recurrence rate of 1.5 %. With a median follow-up of 29 months, the 5-year recurrence rates for the TARGIT-A versus EBRT patients were 3.3 and 1.3 %, respectively, \( p = 0.042 \).

Conclusions. With 5.8 years of median follow-up, IOERT appears to have a subset of low risk women for whom IOERT is acceptable. With 29 months of median follow-up the results of IORT with 50-kV devices are promising, but longer follow-up data are required. At the current time, single-fraction IOERT or IORT patients should be treated under strict institutional protocols.

In the preceding report (Part 1) in this issue of the Annals, we outline the rationale for intraoperative radiation therapy (IORT) and begin a critical analysis of the 2 prospective randomized trials currently published. Part 1 discusses the ELIOT Trial, a trial using electrons during surgery as the entire radiation therapy treatment. In this report, we continue with a critical analysis of the TARGIT-A Trial, a trial that used 50-kV x-rays rather than electrons.

METHODS

See Part I for methods used in the analysis.

TARGIT-A Trial

Overview The TARGIT-A Trial randomized 3,451 patients either to standard EBRT treatment or to TARGIT-A. Eligibility criteria were age ≥ 45 years, tumor size ≤ 3.5 cm, N0-1, M0, and unifocal invasive ductal carcinoma. If the participating institution determined the patient was at high risk for recurrence, an additional 5 weeks of EBRT was given, calling this “risk-adapted IORT.” The Trial began in March 2000. Beginning in 2004, approximately 30 % of the patients had TARGIT-A after final pathology in a second surgical
| STUDY            | Median Follow-up | Local recurrences | Any breast event |         |         |         |         |         |         |         |
|------------------|------------------|--------------------|------------------|---------|---------|---------|---------|---------|---------|---------|
|                  |                  | Target | EBRT | Total | % Diff. | p value | Target | EBRT | % Diff. | p value |
| Lancet 2010      | 25 months        | 6      | 5    | 11    | 0.25    | NS      | 10     | 8    | NS      | NS      |
| SABCS 2011       | 32 months        | NS     | NS   | 23    | NS      | NS      | Not Stated |
| SABCS 2012       | 29 months        | 23     | 11   | 34    | 2.01    | 0.042   | 69     | 48   | 2.5     | 0.053   |
| Lancet 2013      | 29 months        |         |      |       |         |         |         |       |         |         |
|                  |                  | Local recurrences: total cohort | Any other breast event: total cohort |         |         |         |         |         |         |         |
|                  |                  | Target | EBRT | %     | p value | Target | EBRT | %     | p value |         |
|                  |                  | 23     | 3.3  | 11    | 1.3     | 0.042   | 46     | 4.9  | 37      | 4.4     | NS      |
|                  |                  | Local recurrences: pre-pathology group | Any other breast event: pre-pathology group |         |         |         |         |         |         |         |
|                  |                  | Target | EBRT | %     | p value | Target | EBRT | %     | p value |         |
|                  |                  | 10     | 2.1  | 6     | 1.1     | 0.31    | 29     | 4.8  | 25      | 4.7     | 0.72    |
|                  |                  | Local recurrences: post-pathology group | Any other breast event: post-pathology group |         |         |         |         |         |         |         |
|                  |                  | Target | EBRT | %     | p value | Target | EBRT | %     | p value |         |
|                  |                  | 13     | 5.4  | 5     | 1.7     | 0.069   | 17     | 5.2  | 12      | 3.7     | NS      |

| Loco-regional Recurrences\(^a\) | Total target | Total EBRT | Target pre-pathology | EBRT pre-pathology | Target post-pathology | EBRT post-pathology |
|---------------------------------|--------------|------------|----------------------|--------------------|-----------------------|---------------------|
| (\(p\) values NS in Lancet 2013)| 4.2% \(N = 31\) | 2.0% \(N = 17\) | 3.1% | 2.0% | 6.2% | 2.0% |

| Regional recurrences | 1.1% | 0.9% |
| Distant recurrences | 3.9% | 3.2% |
| All recurrences\(^b\) | 8.2% | 5.7% | 6.9% | 5.8% | 10.4% | 5.4% |
| (\(p\) values NS in Lancet 2013) | 69 | 48 | 39 | 31 | 30 | 17 |

| Lancet 2013-Appendix | Pre-pathology targit only \((N = 793)\) | Pre-pathology Target + EBRT \((N = 219)\) | Post-pathology targit only \((N = 539)\) |
|----------------------|------------------------------------------|------------------------------------------|------------------------------------------|
| 5-year projected recurrence | 2.7% | 0.9% | 5.9% |

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NS not stated

Lancet 2010: No metastatic events reported. 7 LRR reported. SABCS 2011 Poster: Results kept blinded. Only total number of local recurrences reported. SABCS 2012 Presentation: Targit recurrence was 3.3%, HR = 2.05 (1.01–4.25). Lancet 2013: Distant recurrences and regional recurrences not reported separately.

Total Targit plus EBRT metastases = 62 from SABCS 2012 Presentation

\(^a\) \(p\) values NS in Lancet 2013, but given as .02, HR = 2.2 (1.2–4.2) at SABCS 2012 for total cohort

\(^b\) \(p\) values NS in Lancet 2013, but given as .053, HR = 1.44 (.99–2.08) at SABCS 2012 for total cohort
procedure about 30 days after the original surgery. This group was designated the “postpathology” group as opposed to the “prepathology” group who received TARGIT-A during initial tumor surgery. The results for these different patient cohorts are shown in Table 1.

**Technique** In the prepathology TARGIT-A patients, following tumor excision, an appropriately sized spherical applicator was placed in the tumor bed. Purse string sutures were used to approximate breast tissue at risk to the applicator. Radiation was delivered over 20–45 min to the tumor bed, which received 20 Gy at the surface of the applicator and attenuated to 5–7 Gy at 1-cm depth. If risk factors were found at the time of surgery or postoperatively, when final pathology was available, the 20 Gy TARGIT treatment was considered as a boost, and patients received an additional 50 Gy equivalent of EBRT, delivered over 3–5 weeks, depending on the institutional preference. Institutions were free to determine what risk factors required additional EBRT.

The postpathology TARGIT-A patients received 20 Gy irradiation after final pathology determined no risk.

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**FIG. 1** 5-year Kaplan–Meier projections for recurrences from TARGIT-A treated patients vs EBRT treated patients. 
(a) Ipsilateral breast recurrence. 
(b) Overall breast recurrence. 
(c) Prepathology, local recurrence. 
(d) Postpathology, local recurrence. Adapted from Figs. 2 and 3 in Lancet7

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| Technique | Overall breast recurrence, p=0.053 (ipsilateral, contralateral, axilla and distant) Presented at SABCS, but not in Lancet 2013 |
|-----------|--------------------------------------------------------------------------------------------------------------------------|
|           | IBTR, 3.3% Targit, 1.3% EBRT, p=0.042 |
|           | IBTR, pre-pathology |
|           | 2.1% Targit, 1.1% EBRT, p=0.31 |
|           | IBTR, post-pathology |
|           | 5.4% Targit, 1.7% EBRT, p=0.069 |

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| Recurrence | ipsilateral, contralateral, axilla and distant |
|------------|------------------------------------------------|
| Prepathology | Overall breast recurrence, p=0.053 (ipsilateral, contralateral, axilla and distant) Presented at SABCS, but not in Lancet 2013 |
|            | IBTR, 3.3% Targit, 1.3% EBRT, p=0.042 |
|            | IBTR, pre-pathology |
|            | 2.1% Targit, 1.1% EBRT, p=0.31 |
|            | IBTR, post-pathology |
|            | 5.4% Targit, 1.7% EBRT, p=0.069 |
factors, typically within 30 days of surgical tumor removal.

The EBRT patients, whether prepathology or postpathology, received 3–5 weeks of 50 Gy equivalent EBRT ± boost depending on the institutional preference.

Complications Wound complications were similar between groups, but grade 3 or 4 skin complications were significantly reduced with TARGIT (4 of 1720) vs EBRT (13 of 1731), \( p = 0.029 \).

Regional Failures Regional failures were similar in both groups (8 events for TARGIT vs 6 events for EBRT, \( p = 0.6 \)).

**Results** At 29 months of median follow-up, the 5-year risk of local recurrence was 1.3 % for EBRT and 3.3 % for all TARGIT-A patients (\( p = 0.042 \)). Target A prepathology patients had a 5-year risk of 2.1 %. Postpathology patients had a 5-year risk of 5.7 %.

Overall recurrence (ipsilateral breast, contralateral breast, axilla, and distant) showed a worsening trend for TARGIT A compared with EBRT: 69 events vs 48 events (\( p = 0.053 \)). Both postpathology and prepathology TARGIT-A patients had more local recurrences than the EBRT patients, although the difference was not statistically significant. Postpathology patients exceeded the Trial’s preset noninferiority margin of 2.5 % (5.4 vs 1.7 %, \( p = 0.069 \)); prepathology patients did not (2.1 vs 1.0 %, \( p = 0.31 \)). Approximately 21 % of prepathology patients who received TARGIT-A also had 5 weeks of EBRT because of risk factors determined at the time of surgery or when final histopathology was available. Patients who received only TARGIT-A had 3 times the recurrence rate of those who received TARGIT-A plus 5 weeks of EBRT (2.7 vs 0.9 %). This difference was not significant, but no \( p \) value was provided. Ipsilateral breast recurrence rates for all patients, for prepathology and postpathology patients, and for any breast recurrence are shown in Fig. 1.

**Survival** Breast cancer mortality was similar for TARGIT (2.6 %) vs EBRT (1.9 %), \( p = 0.56 \). TARGIT resulted in significantly fewer non-breast-cancer deaths 1.4 % (\( n = 17 \)) vs 3.5 % (\( n = 35 \)), \( p = 0.0086 \). This was due to fewer deaths from cardiovascular causes and other cancers. Overall mortality was 3.9 % for TARGIT versus 5.3 % for EBRT, \( p = 0.099 \).

**DISCUSSION**

Between March 2000 and April 2010 2,232 patients were accrued, sufficient for proof of noninferiority. Results were reported 3 months after completion of accrual when the median follow-up was 25 months. The authors maintained early publication was justified because proof of noninferiority required only 585 patients, and they had reached that number with a 4.6-year median follow-up. Also they said peak recurrences for breast cancer occur in years 2 and 3, offering in support that no recurrences were seen in year 4. At that time, critics expressed concern mainly about the immaturity of the data. Accrual and randomization of 1,219 additional patients continued until June 2012, increasing the Trial population to 3,451 patients, resulting in a median follow-up of just 29 months.

The TARGIT-A update shows recurrences in both the TARGIT and EBRT groups in year 4. At the time of the update, the 5 EBRT recurrences initially reported more than doubled to 11, and the six initial TARGIT recurrences had almost quadrupled to 23, questioning the claim of a recurrence peak at 2 or 3 years. The results of the TARGIT-A trial, with a median follow-up (FU) of 29 months, is still well below the median time when breast recurrences can be expected, especially since more than 90 % of TARGIT-A women were estrogen receptor positive, and at least 65 % received adjuvant hormonal therapy, a treatment well-known to delay recurrence in ER + women.

The authors used binomial proportion statistics to show equivalence between the mature cohort (2,232 patients, median FU = 3 years, 7 months), the earliest cohort (1,222 patients, median FU = 5 years), and the total cohort (3,451 patients, median FU = 2 years 5 months). Haviland points out that binomial proportion statistics is invalid for follow-ups less than 5 years and that the appropriate statistical methodology is survival analysis for local recurrence. Only 18 % of patients had a FU of 5 years in the TARGIT-A update. Haviland estimates the hazard ratio for the reported local recurrence rates and calculates the local recurrence rate for TARGIT-A could be as high as 3 times TARGIT.
7.1 %, far exceeding the noninferiority margin of 2.5 %
established by the trial.

The initial TARGIT-A publication did not differentiate
between prepathology and postpathology patients or Targit
boost patients.\textsuperscript{1} The TARGIT update shows these strata are
not equivalent, with postpathology having higher local
recurrence rates than prepathology (Table 2), despite
postpathology patients presumably being lower risk as the
treatment was delivered in a second operation after final
pathology.\textsuperscript{7} The authors attribute the difference either to
delay in wound fluid suppression of tumor cells, since there
is a delay of radiation in postpathology TARGIT, or to a
geometric miss when inserting the applicator postsurgery.
While geometric miss might partially explain the results, it
is not the likely a major cause of their findings. The IORT
Intrabeam boost study of 299 patients reported no difference
in recurrence rates between prepathology and
postpathology patients.\textsuperscript{11} The 5-year recurrence rate for all
patients was 1.73 %. The authors do not report the median
applicator size used in the prepathology and postpathology
patients, but if the median sizes reported in other Intrabeam
publications are used, it is likely that postpathology
patients had irradiated tissue volumes less than half the
volumes in prepathology patients.\textsuperscript{11,12} In IORT boost,
EBRT can compensate for the smaller volume irradiated in
the postpathology patients. One can also see this trend in
the prepathology TARGIT patients since TARGIT plus
EBRT has three times fewer local recurrences than TARGIT
alone even though those who also received 5 weeks of
EBRT were presumably at higher risk (Table 2).

The authors note that the difference in IBTR for all
patients is still within their absolute noninferiority margin
of 2.5 % (Fig. 1a).\textsuperscript{7} Cuzick cautions that the authors have
misused the noninferiority criterion, which requires the
upper confidence interval (CI) be less than the predefined
noninferiority level of 2.5 %.\textsuperscript{13} In the TARGIT-A update,
the upper CI was 5.1 %, throwing doubt on their assertion
of noninferiority.\textsuperscript{7} Looking at the divergence of slopes in
Fig. 1a, it appears likely that the 2.5 % noninferiority
Criterion for IBTR will be exceeded irrespective of the CI
upper limit.

Overall breast recurrence rates in the TARGIT group
also exceeded rates in the EBRT group (Fig. 1b), a
difference at borderline statistical significance ($p = 0.053$).\textsuperscript{14}
While the difference in breast cancer deaths with TARGIT
vs EBRT is not significant (20 deaths, 2.6 % vs. 16 deaths,
1.9 %, $p = 0.56$), these higher recurrence rates with short
follow-up suggests more follow-up is needed.

Follow-up may also be too short to determine whether
prepathology TARGIT patients will ultimately do better
than the entire TARGIT cohort. The difference between
this favorable TARGIT cohort and the EBRT group is
1.0 %, with a median follow-up of 29 months, compared
with a difference of .25 % between the TARGIT group and
the EBRT group in the initial publication.\textsuperscript{1,7}

The TARGIT study involved 33 centers in 11 countries and
lasted more than 12 years. A large multi-institutional study
such as TARGIT-A demands a high level of control and
standardization. However, in TARGIT-A, each center treated
the EBRT group according to its own institutional guidelines
and could determine its own criteria for which patients would
receive TARGIT boost rather than TARGIT APBI.

Sperk et al. analyzed recurrences in the Mannheim
cohort of TARGIT-A patients.\textsuperscript{15} Among 54 TARGIT-A
patients, 37 % were converted from TARGIT APBI to
TARGIT Boost because of risk factors Sperk et al. chose
for conversion, which included larger tumors (>2 cm) with
narrower margins (<10 mm). With a median follow-up of
40 months, they report no recurrences in the 34 patients
who received TARGIT APBI. Notably, 80 % of their
patients also received adjuvant endocrine therapy, which
could delay the appearance of recurrences. Nevertheless, if
these good results are sustained with longer follow-up and
can be replicated by other centers, it is possible that T1
tumors and wide excision surgery with adjuvant endocrine
therapy could form a basis for “risk-adapted” TARGIT
treatment. The variability of standards from center to
center in the TARGIT-A Trial makes it more difficult to
identify which cohort of women might benefit from this
treatment strategy.

Prepathology women meeting the general TARGIT-A
inclusion criteria appear to be the best candidates. How-
ever, at least 20 % of women who receive TARGIT
treatment will also require 5 weeks of EBRT. Because the
TARGIT-A study allowed treatment centers to determine
the risk factors that required an additional 5 weeks of
treatment, the Trial provides no guidance to new adopters
as to when it is appropriate to add additional treatment.

The volume of tissue irradiated with the TARGIT
technique is of concern because dose decreases rapidly
with distance from the applicator surface. Even assuming
favorable radiobiological equivalence, only tissue within a
few mm of the applicator surface receives as much as a
50-Gy EBRT equivalent dose.

In the Milan III Trial, quadrantectomy alone was
insufficient to achieve local control in early-stage breast
cancer, even though 20 mm of tissue beyond the tumor was
excised in all directions.\textsuperscript{16} At 10 years, local recurrence
rates in patients receiving quadrantectomy alone vs those
also receiving quadrantectomy plus 5 weeks of EBRT was
23.5 versus 5.8 %, respectively, with the difference less in
older patients.

A multicenter randomized trial in women older than
55 years compared wide excision surgery alone (1 cm clear
margins) with wide excision surgery plus 5 weeks of
EBRT with an EBRT boost.\textsuperscript{17} Almost all patients received
adjuvant hormonal therapy. With a median follow-up of 9 years, the local recurrence rates were 4.4% for excision alone versus 3.4% for excision plus radiation therapy, \( p = \text{NS} \).

In TARGIT-A, the combination of surgical excision and effective radiation treatment depth is less than in Milan III, and in some cases, even less than 10 mm total. At 29 months median follow-up, the TARGIT-A postpathology (all of whom received a single-dose treatment in a second procedure) had local recurrence rates of 5.7%, whereas prepathology patients (21% of whom also received 5 weeks of WBI) had local recurrence rates of 2.1%.

Fewer deaths were observed in the TARGIT arm than the EBRT arm, 37 versus 51, \( p = 0.008 \) (Table 3). The TARGIT authors assert that TARGIT treatment, while resulting in higher local recurrence rates, leads to an overall improvement in survival due to fewer non-breast cancer deaths. This conclusion is one of the main findings in the TARGIT-A update publication.\(^7\) The authors recommend that clinicians advise patients that while TARGIT bears a higher risk of local recurrence, TARGIT may decrease overall mortality by 2.3%.

Harness et al. and Yarnold et al. argue that it is impossible for the 12-year-old Targit study, with a median follow-up of 29 months, to impact other cancer deaths, since the latency period for inducing non-breast cancers from breast treatment is known to be 15–20 years.\(^1\)\(^8\)–\(^2\)\(^2\) Mackenzie et al., Yarnold et al., and Harness et al. argue that Vaidya et al.’s assertion (fewer cardiac deaths from TARGIT) is inconsistent with the Darby study, the very study cited \(^1\) in support of this claim.\(^1\)\(^7\)\(^1\)–\(^2\)\(^2\) Mackenzie et al. suggest differences in baseline cardiac risk factors in the study groups are the most likely explanation for finding more cardiac deaths in the EBRT arm.\(^2\)\(^0\) Vaidya et al. concede that cardiovascular assessment was not recorded prior to study entry, but speculates that IORT of the tumor bed might have systemic beneficial effects that contribute to reduction in non-breast cancer mortality.\(^2\)\(^2\) However, this theory was not confirmed in the more mature ELIOT study, which showed no differences in non-breast cancers and overall survival, even out to 10 years of follow-up.\(^2\)\(^3\)

### TARGIT-A CONCLUSIONS

The TARGIT-A trial, like the ELIOT Trial, included patients that today would not be considered the best choice for APBI. TARGIT-A has contributed to our understanding of whether a 1-day treatment may be possible, this time using 50-kV X-rays. With 29 months of median follow-up, the TARGIT Data are still immature and risk-adapted IORT with 50-kV X-rays is still too early in follow-up to select the subset of women whose local control will be within their noninferiority criteria margin of 2.5%. Prepathology patients who meet the TARGIT-A inclusion criteria appear to be the best candidates and, at this point, show encouraging results. Until the data are more mature, 50-kV patients should be treated under strict institutional protocols. When long-term results are available, it is likely there will be a higher overall recurrence rate for TARGIT when compared with EBRT, but, as with ELIOT, we may be able to select subgroups of favorable patients where this

|                  | TARGIT | EBRT | TARGIT | EBRT | TARGIT | EBRT | TARGIT | EBRT | TARGIT | EBRT |
|------------------|--------|------|--------|------|--------|------|--------|------|--------|------|
| Breast cancer    | 20     | 16   | 20 (2.6 %) | 16 (1.9 %) | 17 (3.3 %) | 15 (2.7 %) | 3 (1.2 %) | 1 (0.5 %) |
| Other cancers    | 8      | 16   | 8      | 8    | 8      | 8    | 8      | 8    | 8      | 8    |
| Cardiac death    | 2      | 8    | 2      | 8    | NS     | NS   | NS     | NS   | NS     | NS   |
| Strokes          | 0      | 2    | 0      | 2    | 0      | 2    | 0      | 2    | 0      | 2    |
| Ischemic bowel   | 0      | 1    | 0      | 1    | 0      | 1    | 0      | 1    | 0      | 1    |
| Other deaths     | 7      | 8    | 22*    | 24a  | 22*    | 24a  | 22*    | 24a  | 22*    | 24a  |

Adapted from Table 2, Lancet\(^7\) w/Breast Cancer Deaths added

* Death due to breast cancer and cardiac events together

\( \text{NS} \) not stated
difference is small and acceptable. How much additional risk of local recurrence is acceptable will vary with patients and the situation in which they find themselves.

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