Ann Surg Oncol (2016) 23:1796–1798
DOI 10.1245/s10434-016-5129-z

Annals of
SURGICAL ONCOLOGY
OFFICIAL JOURNAL OF THE SOCIETY OF SURGICAL ONCOLOGY

CrossMark

EDITORIAL – BREAST ONCOLOGY

Intraoperative Radiation Therapy in Breast Cancer: Still Not Ready for Prime Time

Chirag Shah, MD[1], Jessica Wobb, MD[2], and Atif Khan, MD[3]

[1]Department of Radiation Oncology, Taussig Cancer Institute, Cleveland Clinic, Cleveland, OH; [2]Department of Radiation Oncology, Ohio State University, Columbus, OH; [3]Department of Radiation Oncology, Robert Wood Johnson University Hospital/Cancer Institute of New Jersey, New Brunswick, NJ

Over the past two decades, radiation therapy techniques and strategies have continued to evolve beyond standard fractionation (1.8–2.0 Gy per fraction) whole breast irradiation (WBI), which delivers treatment over 5–6½ weeks. These include hypofractionated (increased dose per fraction) whole breast irradiation (AWBI), which allows for the whole breast to be treated in 3 weeks and partial breast techniques, including accelerated partial breast irradiation (APBI) and intraoperative radiation therapy (IORT), which target only the tumor bed and a rim or normal tissue surrounding it. Approximately 2 years ago, we presented an editorial evaluating the data supporting IORT and felt that based on the data available at that time that IORT was investigational and not appropriate for off-trial utilization.[1] This editorial was met with resistance by some groups who felt the data available supported adoption of IORT.[2] Since that time, data have continued to evolve and controversy still exists regarding the role of IORT in the management of women with early-stage breast cancer.

The strongest evidence regarding IORT comes from two randomized trials that compared IORT and standard WBI. The TARGIT-A (Targeted Intraoperative Radiotherapy) Trial was a randomized, "noninferiority" study that enrolled 3451 women older than age 45 years with unifocal invasive ductal carcinoma following wide local excision. IORT was delivered at a dose of 20 Gy using 50-kv photons, whereas WBI was delivered to a dose of 40–56 Gy with or without boost. Of note, IORT could be delivered at the time of lumpectomy (pre-pathology cohort, 2/3 patients) or after lumpectomy (post-pathology cohort, 1/3 patients). WBI was given to IORT patients with close surgical margins, extensive DCIS, lobular carcinomas, and positive lymph nodes (21.6 % pre-pathology, 3.6 % post-pathology, 15.2 % overall). Of note, while 5-year outcomes were published, median follow-up was only 29 months and at that time IORT was associated with a statistically significant increase in local recurrence (3.3 vs. 1.3 %, $p = 0.04$); further, in the post-pathology group, the increase exceeded the 2.5 % noninferiority threshold (5.4 vs. 1.7 %, $p = 0.07$).[3] The updated results have sparked significant controversy in the surgical and radiation oncology communities with concern raised regarding the statistical methodology of the trial including "misuse of the noninferiority criterion," a focus on the pre-pathology cohort rather than all patients, and significant numbers of patients lost to follow-up with an already shortened follow-up.[4] Based on these findings, several authors have stated that IORT is not appropriate therapy off-protocol at this time while others disagree.[4–7]

The second randomized IORT trial was the ELIOT trial, which utilized intraoperative electrons; 1305 patients were randomized to WBI (50 Gy with 10 Gy boost) or IORT (21 Gy with 6–9 MeV electrons) with no supplementary WBI utilized. With a median follow-up of 5.8 years, IORT was associated with an increase in ipsilateral breast tumor recurrences (4.4 vs. 0.4 %, $p < 0.0001$).[8] Taken together, both randomized trials have demonstrated higher rates of local recurrence compared with standard WBI. In light of these findings, a question that emerges is whether IORT is better than endocrine therapy alone following breast-conserving surgery. For example, the CALGB 9343 trial had a 4 % rate of local recurrence at 5 years (95 % confidence interval [CI] 2–7 %), whereas the TARGIT trial had a

© Society of Surgical Oncology 2016

First Received: 23 December 2015;
Published Online: 22 February 2016

C. Shah, MD
e-mail: csshah27@hotmail.com

3.3 % rate of local recurrence at 5 years (95 % CI 2.1–5.1 %, follow-up 28 months), with 15 % of patients receiving WBI.[3,9] Similarly, the 5-year local recurrence rate with ELIOT was 4.4 % (95 % CI 2.7–6.1 %) with a hazard ratio of 9.3 compared with standard WBI.[8] In light of a continuing rise in the rate of local recurrence and difference in local control compared with WBI in the CALGB trial with excision alone, concern exists regarding a similar increase in local recurrences and increasing difference with WBI in the IORT cohort in years 5–10 following treatment.

As noted above, IORT is not the only partial breast technique available to patients, with APBI representing a technique with multiple randomized trials and longer follow-up. While there are some who look to minimize the difference in recurrence rates seen in the IORT trials and consider them low overall, it should be noted that none of the four randomized APBI trials to date have found a significant increase in local recurrence compared with WBI with 5-year or greater follow-up.[10–13] Recently, Strnad et al. published results of the GEC-ESTRO trial, which randomized 1184 patients with early-stage breast cancer (Stage 0–IIA) to WBI or APBI delivered with interstitial brachytherapy. With a median follow-up of 6.6 years (compared with the 2.5 years with TARGIT), no difference in the rates of local recurrence were noted (1.4 % APBI vs. 0.9 % WBI, $p = 0.42$). Compared with the IORT trials, this trial reflects a superior noninferiority design which utilized an analysis based on treatment delivered and included secondary sensitivity analyses to confirm the consistency of the data. It also should be noted that differences in delivery and dosimetry exist between APBI and IORT. APBI delivers full dose to a 1-cm margin of tissue or greater surrounding the lumpectomy cavity (1 cm applicator, 2 cm interstitial, 2–2.5 cm external beam) while IORT delivered with low-energy X-rays (most commonly utilized in the United States) delivers roughly a quarter of the prescription dose (5 Gy/1 fraction) at 1 cm.[10–14] This dose is felt to be insufficient and may be why higher rates of local recurrence are noted particularly when one evaluates pathologic data demonstrating most residual disease is within 1 cm of the lumpectomy cavity.[15] Similarly, image guidance is lacking with many IORT techniques and there exists a lack of dosimetric data or planning data compared with APBI. Taken together, unlike IORT, the four randomized APBI trials support the use of APBI off-protocol in appropriately selected women. For APBI, the majority of randomized data comes from interstitial brachytherapy (National Institute of Oncology Hungary, GEC-ESTRO) and external beam techniques (RAPID, Hospital de la Esperanza, University of Florence); whereas randomized data regarding alternative techniques, such as applicator-based brachytherapy, has yet to be published, outcomes regarding such cohorts are expected in the years to come (e.g., NSABP B-39) and should help to define optimal treatment techniques and target volumes. Evidence-based guidelines support the use of such applicator-based techniques though clinicians should understand that some differences in dosimetry and target volumes exist compared with interstitial and external beam techniques.

Also, three randomized trials comparing hypofractionated WBI with standard WBI have demonstrated no difference in local recurrence.[16,17] One advantage of IORT compared with alternatives is a reduction in treatment duration; however, APBI and AWBI studies demonstrate treatment duration can be reduced to 1–3 weeks while not compromising local control. Another potential advantage of IORT is the cost savings associated as noted by several cost analyses.[18,19] However, these studies either did not include the cost of recurrences or projected rates of local recurrence below those seen from the randomized trials available to date. When factoring in the cost of recurrences, it appears that IORT is not the cost savings once projected and that is without factoring in the quality of life detriment and associated toxicities associated with the treatment of recurrences.[20]

In summary, after reviewing the data available, several conclusions can be drawn: (1) IORT, compared with standard WBI, is associated with higher rates of recurrence with limited long term follow-up; (2) Concerns exist regarding the statistical methodology of the TARGIT-A trial limiting its clinical applicability; (3) While IORT may represent a technique that can reduce the duration of radiation therapy, alternatives including AWBI and APBI allow for the completion in 1–3 weeks without the need for remedial WBI (15 % of TARGIT cases) or higher rates of recurrence; (4) Cost savings projected with IORT must be tempered and future studies are needed to factor in the cost of recurrences, as well the toxicities and impairment in quality of life. In the United States, IORT has continued to disseminate into clinical practice with limited data available on the number of centers utilizing the technique at this time (per TARGIT there are 42 cities in the United States where TARGIT is available). At this time, although more data are available, the conclusion remains the same: intraoperative radiation therapy in breast cancer is still not ready for primetime and the increased utilization and availability is not supported by clinical outcomes available to date. That being said, this is not the final chapter for IORT as further study is required: (1) longer follow-up is need from the TARGIT and ELIOT studies, and (2) comparisons of endocrine therapy alone to IORT are limited (TARGIT-E) and may represent an area to consider. What remains certain is that controversy will continue to exist regarding the technique.

CONFLICT OF INTEREST Chirag Shah-Previous consultant/speaker Cianna Medical, Atif Khan-consultant Elekta, advisory board Vertex Pharmaceuticals.

REFERENCES

1. Shah C, Khan AJ, Arthur D, et al. Intraoperative radiation therapy in breast cancer: not ready for prime time. *Ann Surg Oncol.* 2014;21:351–3.
2. Holmes DR. Intraoperative radiotherapy of the breast for early-stage breast cancer: ready for primetime. *Breast J.* 2015;21:181–4.
3. Vaidya JS, Wenz F, Bulsara M, et al. Risk-adapted targeted intraoperative radiotherapy versus whole-breast radiotherapy for breast cancer: 5-year results for local control and overall survival from the TARGIT-A randomised trial. *Lancet.* 2014;383:603–13.
4. Cuzick J. Radiotherapy for breast cancer, the TARGIT-A trial. *Lancet.* 2014;383:1716.
5. Hepel J, Wazer DE. A flawed study should not define a new standard of care. *Int J Radiat Oncol Biol Phys.* 2015;91:255–7.
6. Vaidya JS, Bulsara M, Wenz F, et al. Pride, prejudice, or science: attitudes towards the results of the TARGIT-A trial of targeted intraoperative radiation therapy in breast cancer. *Int J Radiat Oncol Biol Phys.* 2015;92:491–7.
7. Harris EE, Small W Jr, Holmes D, et al. In Regard to Hepel and Wazer. *Int J Radiat Oncol Biol Phys.* 2015;92:955–7.
8. Veronesi U, Orecchia R, Masonneuve P, et al. Intraoperative radiotherapy versus external beam radiotherapy for early breast cancer (ELIOT): a randomised controlled equivalence trial. *Lancet Oncol.* 2013;14:1269–77.
9. Hughes KS, Schnaper LA, Bellon JR, et al. Lumpectomy plus tamoxifen with or without irradiation in women age 70 years or older with early breast cancer: long-term follow-up of CALGB 9343. *J Clin Oncol.* 2013;31:2382–7.
10. Polgar C, Fodor J, Major T, et al. Breast-conserving therapy with partial or whole breast irradiation: ten-year results of the Budapest randomized trial. *Radiother Oncol.* 2013;108:197–202.
11. Strnad V, Ott OJ, Hildebrandt G, et al. 5-year results of accelerated partial breast irradiation using sole interstitial multicatheter brachytherapy versus whole-breast irradiation with boost after breast-conserving surgery for low-risk invasive and in situ carcinoma of the female breast: a randomised phase 3, non-inferiority trial. *Lancet.* 2015;387:229–38.
12. Rodriguez N, Sanz X, Dengra J, et al. Five-year outcomes, cosmesis, and toxicity with 3-dimensional conformal external beam radiation therapy to deliver accelerated partial breast irradiation. *Int J Radiat Oncol Biol Phys.* 2013;87:1051–7.
13. Livi L, Meattini I, Marrazzo L, et al. Accelerated partial breast irradiation using intensity-modulated radiotherapy versus whole breast irradiation: 5-year survival analysis of a phase 3 randomised controlled trial. *Eur J Cancer.* 2015;51:451–63.
14. Khan AJ, Arthur DW, Vicini FA. On the road to intraoperative radiotherapy: more 'proceed with caution signs.' *Oncology.* 2013;27:113–4.
15. Vicini FA, Kestin LL, Goldstein NS. Defining the clinical target volume for patients with early-stage breast cancer treated with lumpectomy and accelerated partial breast irradiation: a pathologic analysis. *Int J Radiat Oncol Biol Phys.* 2004;60:722–30.
16. Haviland JS, Owen JR, Dewar JA, et al. The UK Standardization of Breast Radiotherapy (START) trials of radiotherapy hypofractionation for treatment of early breast cancer: 10-year follow-up results of two randomised controlled trials. *Lancet Oncol.* 2013;14:1086–94.
17. Whelan TJ, Pignol JP, Levine MN, et al. Long-term results of hypofractionated radiation therapy for breast cancer. *N Engl J Med.* 2010;362:513–20.
18. Alavarado MD, Mohan AJ, Esserman LJ, et al. Cost-effectiveness analysis of intraoperative radiation therapy for early-stage breast cancer. *Ann Surg Oncol.* 2013;20:2873–80.
19. Grobmyer SR, Lightsey JL, Bryant CM, et al. Low-kilovoltage, single-dose intraoperative radiation therapy for breast cancer: results and impact on a multidisciplinary breast cancer program. *J Am Coll Surg.* 2013;216:617–23.
20. Shah C, Badiyan S, Khwaja S, et al. Evaluating radiotherapy options in breast cancer: does intraoperative radiotherapy represent the most cost-efficacious option? *Clin Breast Cancer.* 2014;14:141–6.