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Commentary on "Accelerated partial breast irradiation consensus statement: Update of an ASTRO Evidence-Based Consensus Statement"

Although the new American Society for Radiation Oncology (ASTRO) consensus statement on accelerated partial breast irradiation (APBI) reflects many important changes relative to case selection and inclusion criteria for APBI, we would like to address our concerns specifically regarding the recommendations on the use of low-energy x-ray intraoperative radiation therapy (IORT). The consensus should include a statement that targeted intraoperative radiation therapy (TARGIT) IORT achieves local control similar to external beam radiation therapy (EBRT) with a potential for a survival benefit.[1-4]

Although the panel correctly recognized that the local recurrence rate in prepathology (TARGIT given simultaneously during lumpectomy) stratum was *NOT* significantly different from the whole-breast external beam irradiation (WBI) arm (2.1% vs 1.1%, $P = .31$), the panel gave "greater weight" to the local recurrence rate of the entire IORT cohort (prepathology and postpathology [TARGIT given after lumpectomy as a second procedure by reopening the wound at a median of 37 days after the initial excision] strata combined). Sometimes the devil is in the details. The TARGIT-A trial specified stratification between pre- and postpathology *before randomization* to accommodate different practices in the participating sites.[5] Because the 2 strata were randomized separately, there is little bias that could explain the differing results. Instead, the superior result in the prepathology group is likely explained by avoidance of spatial and temporal miss as well as by data suggesting that biologically IORT inhibits local chemokines that promote local recurrence.[6] Thus, the panel's recommendations regarding IORT should have acknowledged the results for the prespecified analysis for the primary endpoint of IORT treatment in the whole trial (n = 3451, a difference of 2%; $P = .04$), as well the prepathology stratum (n = 2298, a difference of 1%; $P = .31$).[1-3] Results of prepathology TARGIT IORT were clinically and statistically *not* significantly different from EBRT.

The panel neglecting to recognize the identical results of TARGIT IORT vs EBRT in progesterone receptor (PR)-positive patients of the prepathology stratum is surprising in light of their decision to use a subgroup analysis from the Electron Intra Operative Radiation Therapy (ELIOT) trial to validate the use of electron beam IORT.[7,8] A post hoc analysis of a small subgroup of 294 patients meeting the 2009 ASTRO "suitable" criteria[9] in the ELIOT trial (n = 1301) was used to support the panel's recommendations in favor of electron beam IORT. The consensus should therefore also include the outcome of the much larger group of 2298 prespecified subjects in the TARGIT prepathology stratum in which comparable local control was achieved. Furthermore, the 5-year local recurrence rate in the large subgroup of 1625 PR-positive patients, prespecified before unblinding of the data, was 1.4% in the TARGIT and 1.2% in the WBI arm, with a 3.1% improvement in overall survival in the TARGIT patients (Figs 1 and 2) [breast cancer mortality: 1.78% vs 1.98% $P = 0.91$, non-breast-cancer mortality: 1.6% vs. 4.5% $P = 0.04$, overall mortality: 3.3% vs 6.4% $P = 0.08$][1] Comparing the 636 TARGIT-A patients with a median 5-year follow-up to the whole and mature cohorts of the trial notes no evidence of delayed recurrences. These 636 TARGIT-A patients' results (locoregional recurrence, 1.4%) compare well with the post hoc ELIOT good risk subgroup analysis of the 294 ELIOT patients with a

Conflicts of interest: R.D.: personal fees received from Carl Zeiss for US TARGIT Academy Faculty outside the submitted work. S.G.: grants and nonfinancial support from Carl Zeiss outside the submitted work. D.H.: grants and personal fees from Carl Zeiss related to the submitted work. C.L.: royalties from Up-To-Date and speech honoraria from Genomic Health outside the submitted work. A.M.: speech honoraria from Carl Zeiss outside the submitted work. W.S.: honoraria for talk and travel expenses and a grant for the TARGIT US Registry Trial from Carl Zeiss both related to and outside the submitted work. J.T.: honoraria for speeches and travel support for International Steering Committee meetings and conferences where TARGIT data are being presented from Carl Zeiss both related to and outside the submitted work. J.V. honoraria for speeches and travel support for International Steering Committee meetings and conferences where TARGIT data are being presented from Carl Zeiss, both related to and outside the submitted work, and a grant from Photoelectron Corporation from 1996-1999 related to the submitted work. F.W.: grants and personal fees from Carl Zeiss and Elekta related to the submitted work, personal fees from Celgene and Ipsen outside the submitted work, and 2 issued patents with no financial or commercial aspects.

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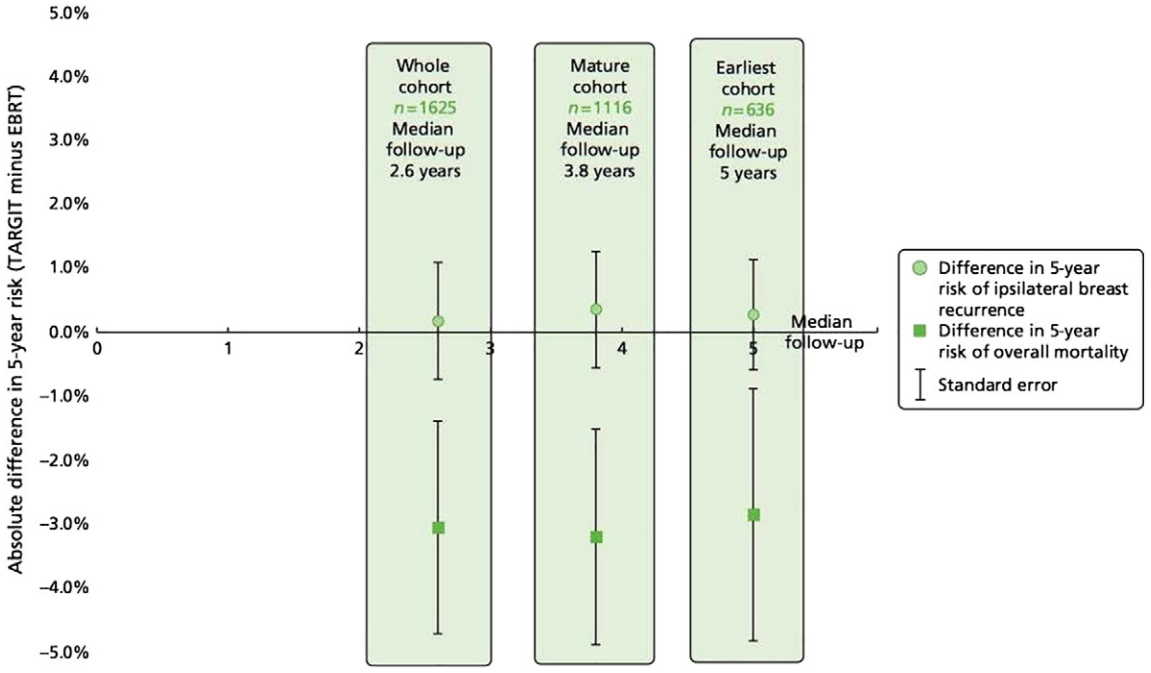

Figure 1 Local recurrence and overall mortality for PR-positive patients in the prepathology targeted intra-operative radiation therapy (TARGIT-A) trial.[1] Note that the mature cohort includes all patients from the earliest cohort and the whole cohort includes all patients from the mature cohort. Reproduced with permission from the National Institute for Health Research Journals Library.

locoregional recurrence rate of 1.5%, both with a median follow-up of 5 years.

While looking at follow-up, one must remember that the effect of radiation therapy on local recurrence is generally in the first 2 to 3 years and disappears after 5 years. The follow-up for the entire TARGIT-A trial dataset included 3451 patients with a median follow-up of 2 years and 5 months. Moreover, the earliest cohort of 1222 patients had a median of 5 years of follow-up. The analysis of the number of events in all patients and this earliest cohort found that the absolute difference (90% confidence interval) in the binomial proportions of local recurrence in the conserved breast was 0.72% (0.2-1.3) and 1.14% (-0.1 to 2.4) with a highly significant *P* value confirming noninferiority.[3] The ELIOT trial[7] included 1305 patients with a median follow-up of 5 years, which is comparable in number to the earliest cohort of patients (n = 1222) in the TARGIT-A trial. More recently, results of the Groupe Européen de Curiethérapie -European Society for Radiotherapy & Oncology phase 3 trial of APBI using interstitial multicatheter brachytherapy[10] used a noninferiority margin of 3%, similar to the 2.5% used in the TARGIT-A trial. Both trials showed no significant difference in local recurrence between the 2 randomized groups as well as lower non-breast cancer mortality.[11] Furthermore, patient-reported quality of life results recently reported that patients treated with IORT have similar self-reported cosmetic outcomes with better breast-related quality of life than patients treated with external beam therapy.[12] We must also recognize the savings to the health care system by using TARGIT, which have been estimated to be at least $1.2 billion in the United States over 5 years.[13]

One cannot ignore that the available evidence has prompted clinicians and patients to use TARGIT IORT in more than 300 major hospitals in 35 countries, including the United States (61 centers, including Loyola University, Cornell University, Georgetown University, University of California San Francisco, Columbia University, Cleveland Clinic, Northwestern, William Beaumont, University of Southern California), Canada, the United Kingdom, France, Germany (60 centers), Italy, Scandinavia, Switzerland, China, Australia (government funded), and New Zealand. More than 20,000 women have been treated successfully worldwide (Fig 3).

An objective consensus statement requires the collaboration and intellectual analysis of all specialty physicians involved in a patient's care. Excellent examples of this approach are the recently reported margin consensus guidelines for ductal carcinoma in situ and invasive cancer, which included representation from the American Society of Radiation Oncology, Society of Surgical Oncology, American Society of Breast Surgeons, and the American Society of Clinical Oncology. This APBI "consensus" statement was created in isolation, despite calls from the leadership of national surgical societies to participate in the data analysis and consensus statement preparation.[14,15]

In summary, we have numerous concerns regarding the selection and interpretation of the data presented and request reconsideration of the entirety of available data and a more balanced interpretation to enable all breast cancer patients to benefit from the best available options. The ASTRO statement should include the high-quality evidence that indicates that low-energy IORT is an excellent option for suitable patients.

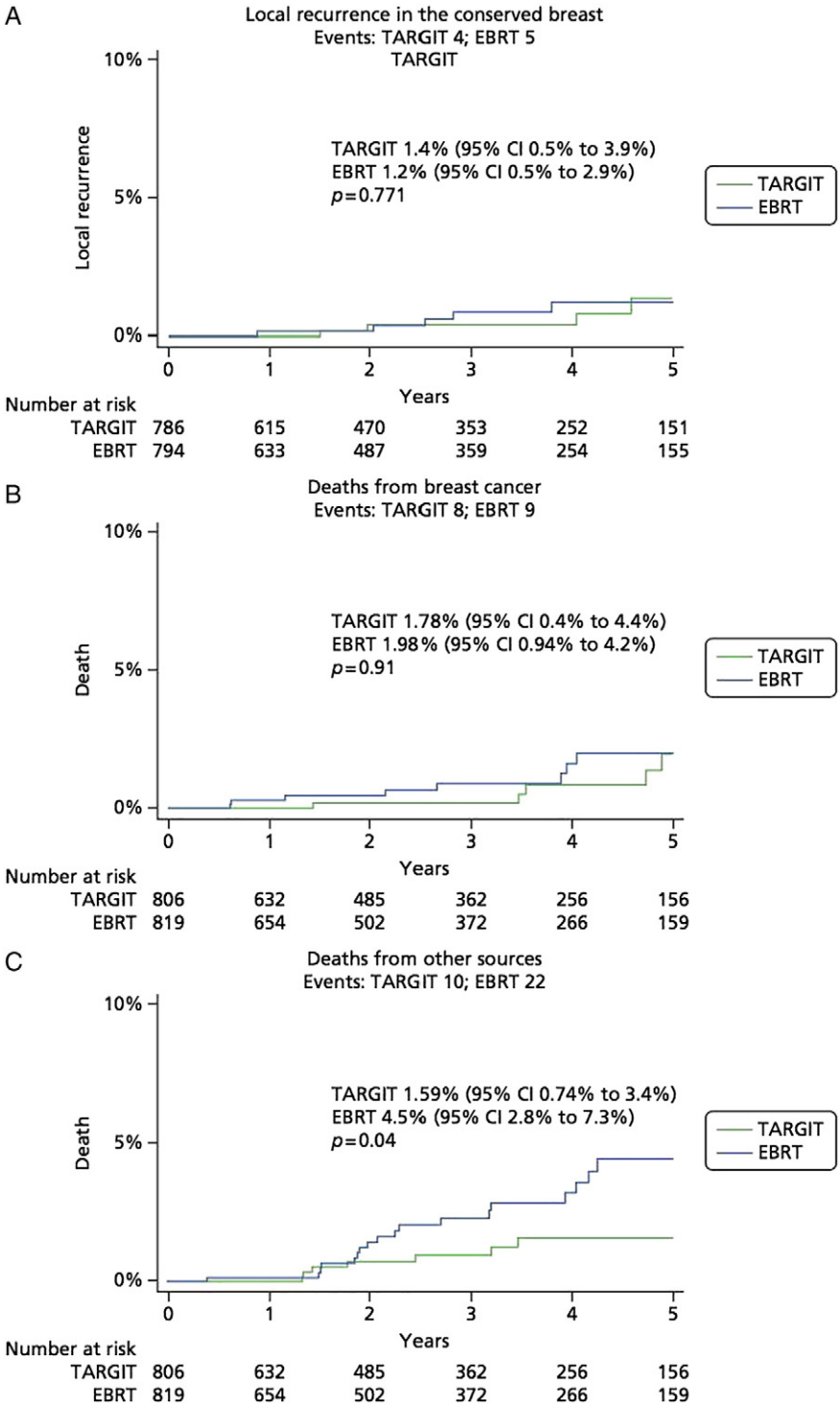

Figure 2 Local recurrence, death from cancer, and death from other causes in the prepathology PR-positive patients in the randomized TARGIT-A trial.[1] Reproduced with permission from the National Institute for Health Research Journals Library. EBRT, external beam radiation therapy. Other abbreviations as in Fig 1.

Figure 3 Countries offering TARGIT intraoperative radiation therapy (IORT) for breast cancer. Reproduced and modified with permission from Carl Zeiss Meditech. Other abbreviations as in Fig 1.

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