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COMMENTARY

Updated ASTRO guidelines on accelerated partial breast irradiation (APBI): to whom can we offer APBI outside a clinical trial?

ANNA M KIRBY, FRCR

Department of Radiotherapy, Royal Marsden NHS Foundation Trust and Institute of Cancer Research, Sutton, UK

Address correspondence to: Dr Anna M Kirby
E-mail: *anna.kirby@rmh.nhs.uk*

ABSTRACT

The American Society of Radiation Oncology has recently updated its guidelines on the role of accelerated partial breast irradiation in the management of breast cancer. This commentary discusses the new recommendations and how we might advise patients in the light of existing data.

Accelerated partial breast irradiation (APBI) describes radiotherapy techniques in which radiation dose is variably restricted to the tumour or tumour bed and surrounding breast tissue as opposed to treating the entirety of the ipsilateral breast glandular tissue. The "accelerated" aspect describes delivering radiotherapy treatment over a shorter overall treatment time than the old standard of 50 Gy in 25 fractions and can include anything from treatment delivered in 15–16 daily fractions, to twice-daily fractionations over ten days, to single dose treatments delivered either intra- or post-operatively. Potential advantages of accelerated partial breast irradiation APBI over whole breast irradiation include the possibility of reduced side-effects (assuming dose and technique are appropriately selected and quality- assured) and increased convenience for patients. However, it is important that this should not be to the detriment of the excellent local control and survival rates achieved in breast cancer patients in recent years. Several large randomized controlled trials of whole versus partial breast irradiation have accrued and matured over the past decade and the American Society of Radiation Oncology (ASTRO) has recently updated its guidelines to reflect the reported results of some of these studies.[1]

DEVELOPMENT OF THE ORIGINAL ASTRO APBI GUIDELINES

In 2009, in the light of burgeoning off-trial use of accelerated partial breast irradiation (APBI) in the United States,[2] the ASTRO Health Services Research Committee convened a Task Force of breast cancer radiotherapy experts to develop consensus guidelines on selection of patients for APBI outside a clinical trial.[3] A systematic literature review was undertaken and recommendations were predominantly based on data from four prospective randomized clinical trials (RCTs) with median follow-up of between 1 and 8 years, together with 10 prospective single-arm studies selected for having follow-up of ≥4 years. Based on the clinicopathological inclusion criteria of patients well-represented in studies reporting ipsilateral breast tumour recurrence (IBTR) rates of <10% at the above time points, a group "suitable" for off-trial APBI was defined. This included females ≥60 years with unifocal T1N0 ER-positive ductal carcinomas, excision margins of ≥2 mm and absence of lymphovascular invasion (LVI) or extensive intraductal component. A "cautionary" group was then defined to include characteristics of females who had been enrolled in the above studies but who were not well-represented, whilst an "unsuitable" group was defined as including characteristics of patients for whom there was little evidence from clinical trials. A review of US APBI usage before and after publication of the ASTRO APBI guidelines[2] suggests that the guidelines were helpful in reducing less appropriate use of APBI delivered using brachytherapy techniques.

Outside the USA, GEC-ESTRO guidelines[4] defined broadly similar groups of females considered to be at low risk of IBTR (and therefore suitable for APBI), intermediate risk of IBTR (and therefore suitable for APBI only in the context of a clinical trial), and high risk of IBTR (for whom the GEC-ESTRO guidelines more definitively suggest that APBI is contraindicated, even in the context of a clinical trial). In the UK, the IMPORT-Low and TARGIT studies were recruiting in

2009, such that patients defined as ASTRO and/or GEC-ESTRO "suitable" for APBI will predominantly have been treated within rather than outside clinical trials. Following completion of accrual to IMPORT Low and TARGIT-A, whole breast irradiation remained the UK standard of care until the 2016 Royal College of Radiologists' (RCR) Breast RT Consensus Guidelines[5] defined a group suitable for off-trial use of APBI (see below).

Update of ASTRO APBI guidelines I: review of "suitable" criteria

The original ASTRO APBI guidelines acknowledged that they were heavily reliant upon data from prospective single-arm studies. The most recent update now includes data from five additional RCTs and reconsiders eligibility criteria for off-trial use of APBI as well as newly considering the role of intra-operative radiotherapy (IORT).

In the light of three RCTs of WBI versus APBI,[6–8] the ASTRO APBI TaskForce reconsidered the age criterion for treating patients with APBI outside a clinical trial. The largest of these RCTs, the GEC-ESTRO trial, randomized females of 40 years or above to WBI plus a tumour bed boost versus APBI delivered using multicatheter brachytherapy.[8] The 5 year risk of ipsilateral breast tumour recurrence (IBTR) was <2% in both arms of the study but only 14% of patients were under 50 years. With the Hungarian and Italian RCTs also recruiting females >40 years and reporting similarly low recurrence rates, again with females <50 years less well-represented, the Task-Force recommended that females of ≥50 years may now be included in the group considered "suitable" for APBI outside a clinical trial. Females aged 40 to 49 are now included in the "cautionary" group and females of <40 years in the "unsuitable" group. Results of the IMPORT Low trial have since been published[9] and support the adjustment of the suitable versus cautionary age threshold. IMPORT Low randomized 2018 females between whole breast irradiation (40 Gy/15 fractions), reduced field radiotherapy (36 Gy/15 fractions to whole breast and 40 Gy/15 fractions to partial breast) and partial breast radiotherapy (40 Gy/15 fractions to partial breast only), all delivered using simple intensity-modulated tangential external beam radiotherapy. Females aged ≥50 years were included and the IBTR rates were 1.1, 0.2 and 0.5% for the whole, reduced and partial groups respectively.

The updated ASTRO APBI guidelines also review the suitability of patients with ductal carcinoma *in-situ* (DCIS) for partial breast irradiation (PBI). They refer to data from RCTs of radiotherapy versus observation in females who underwent breast conservation surgery (BCS) for screen-detected low- to intermediate-grade DCIS, ≤25 mm in size and with ≥3 mm margins, and highlight 7-year IBTR rates of 6–7% in patients treated with surgery alone. A pooled analysis of females meeting these inclusion criteria and treated with APBI reported a 2.6% risk of IBTR at 5 years. Based on the low recurrence rates with surgery alone and low recurrence rates in single-arm prospective studies, females with low-risk DCIS are therefore defined as being "suitable" for APBI although the data might alternatively suggest that these females do not need radiotherapy at all.

With regard to excision margins, the updated ASTRO APBI guidelines adhere to the original recommendation for margins of ≥2 mm. This seems reasonable in the light of both the GEC-ESTRO study and the IMPORT-Low studies defining 2 mm as a minimum excision margin, although when using APBI techniques that treat a larger width of tissue around the tumour bed, it may be reasonable to accept a narrower margin in patients with unifocal disease matching dimensions predicted on diagnostic imaging.

The RCR Breast Radiotherapy Consensus Guidelines[5] on eligibility for off-trial APBI largely reflect the inclusion criteria of the IMPORT-Low and GEC-ESTRO studies *i.e.* patients ≥ 50 years with Grade 1–2 disease, T ≤ 3 cm, ER-positive, HER2-negative, N0, but allow for excision margins of at least 1 mm.

Update of ASTRO APBI guidelines II: which patients are suitable for intra-operative radiotherapy (IORT)?

Determination of selection criteria for IORT was considered beyond the scope of the original ASTRO APBI guidelines. However, following publication of results from the Intraoperative Radiotherapy with Electrons (ELIOT)[10] and TARGIT[11] RCTs, the updated guidelines newly considered this point. ELIOT and TARGIT compared WBI against IORT using electrons and photons, respectively. The ELIOT study randomized 1305 females and, at a median follow-up of 5.8 years, the 5-year IBTR was 4.4% in the IORT arm and 0.4% in the WBRT arm albeit that, in an unplanned subgroup analysis, the group of females defined as ASTRO APBI "suitable" had a recurrence rate of only 1.5%. In TARGIT, 3451 females were randomized overall and the 5-year IBTR risk was reported as 3.3% for the IORT arm and 1.3% for the external-beam WBI arm. The authors of the ASTRO guidelines highlight that interpretation of the results of the TARGIT trial is limited by its median follow-up being only 2.4 years and by statistical shortcomings, which are well described in the updated guidelines and elsewhere in the literature.[12–14] The main recommendation from the updated ASTRO guidelines is therefore that, whilst data mature, "patients interested in cancer control equivalent to that achieved with WBI post-lumpectomy for breast conservation should be counseled that in 2 clinical trials the risk of IBTR was higher with IORT [than with WBI]". Consistent with GEC-ESTRO guidelines, it is recommended that intra-operative electron therapy be used only in patients meeting ASTRO APBI "suitable" criteria and that intra-operative photon therapy be used only in a clinical trial or a prospective registry setting.

Update of ASTRO APBI guidelines III: can external-beam APBI be recommended?

The updated ASTRO guidelines preceded the publication of the IMPORT-Low data such that, based on the evidence available at the time of update, they were unable to recommend for or against external beam APBI techniques. IMPORT-Low has since however demonstrated that, at 5 years, patients undergoing external beam PBI delivered using reduced tangential fields to a dose of 40 Gy in 15 fractions reported fewer moderate/marked events in relation to skin change, change in overall

breast appearance, breast shrinkage and breast firmness than did those patients undergoing external beam WBI to the same dose-fractionation schedule.[9]

With regard to the morbidity of other APBI techniques, the GEC-ESTRO group have demonstrated that their interstitial brachytherapy technique delivering 32 Gy in 8 fractions or 30.1 Gy in 7 fractions twice daily results in equivalent cosmetic outcomes to WBI delivered using a schedule of 50 to 50.4 Gy in 1.8 to 2.0 Gy daily fractions over a 5-week period, but with significantly fewer late skin side-effects in the APBI group.[15]

Recommended techniques in the RCR Breast Radiotherapy Consensus Guidelines reflect those used in the GEC-ESTRO and IMPORT Low studies *i.e.* multicatheter interstitial brachytherapy and external beam radiotherapy (using shortened tangents). The RCR guidelines, however, recommend a dose-fractionation schedule of 40 Gy in 15 daily fractions over 3 weeks consistent with the schedule used in the IMPORT Low trial. This also reflects the UK's adoption of this schedule as standard of care for adjuvant breast radiotherapy following the results of the START-B study demonstrating 40 Gy in 15 fractions over 3 weeks to be gentler on normal tissues than a 50 Gy in 25 fraction over 5 week schedule.[16]

HOW TO ADVISE OUR PATIENTS?

Owing to advances in cancer detection and treatment, the number of breast cancer survivors continues to increase and many of these women will live for many decades beyond their breast cancer diagnosis and treatment. Therefore, even with high-quality data demonstrating reassuringly non-inferior local relapse rates from APBI at 5 years, are we really in a position to tell our patients that APBI is a safe alternative to WBI in the longer term? For example, how relevant might the omission of low axillary tissue from the partial breast irradiated volume be to the risk of later axillary and perhaps distant relapse? A retrospective comparison of 4129 patients with pT1N0 breast cancer treated with WBI (n = 2939) and intra-operative electrons (n = 1190) reported a 10-year cumulative risk of axillary relapse of 1.3% with WBI versus 4.0% with IORT.[17] This two-thirds reduction in the risk of axillary relapse with WBI did not translate into any difference in breast-cancer-related survival but, based on long-term survival gains reported in the Early Breast Cancer Trialists' Collaborative Group meta-analysis,[18] a difference in locoregional relapse rates at 10 years may well translate into a survival difference in the longer term. Therefore, even within the ASTRO APBI guideline-defined "suitable" group, the implications of a possible increased risk of relapse later will be very different for a 70-year-old weighing up 10- to 20-year outcomes to a 50-year-old weighing up 30- to 40-year outcomes. Additionally, given that surgical management of the axilla continues on a path of de-escalation with the SOUND (Sentinel Node *vs* Observation After Axillary Ultra-SouND) trial[19] randomizing cT1N0 patients to sentinel node biopsy versus no axillary surgery at all, it will be important to be mindful of the implications of late axillary relapses and not to de-escalate both surgery *and* radiotherapy outside the context of clinical trials.

In the meantime, women will be keen to minimize the side-effects of radiotherapy for breast cancer and, although both the GEC-ESTRO brachytherapy and IMPORT Low trials have demonstrated reduced late normal tissue effects in women undergoing APBI as compared to WBI, the PRIMETIME study[20] is now evaluating whether, in women at the lowest risk of relapse, radiotherapy can be safely omitted such that women in this category can in future be treated with surgery alone, thus avoiding additional side-effects from breast radiotherapy completely.

CONCLUSION

The updated ASTRO APBI guidelines, by including data from more recent Phase III RCTs, more robustly define a group "suitable" for consideration of APBI. The guidelines will be considered by some to be too strict and by others to be too lax, but, as with all guidelines, will need to be evaluated carefully in the context of each patient and her priorities. It is important to consider patient age, likely longevity, and the implications of any later increase in locoregional relapse on long-term survival. Alongside this, whilst it is important to make our patients aware of all treatment options, we should remain wary of overinterpreting or incorrectly extrapolating our data, and continue to present our patients with as clear and balanced a treatment recommendation as possible based on the available evidence.

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