Comparative Effectiveness Review Disposition of Comments Report

Research Review Title: *Partial Breast Irradiation for Breast Cancer*

Draft report available for public comment from July 1, 2022, to July 29, 2022.

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Comments to Draft Report

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Comments on draft reports and the authors' responses to the comments are posted for public viewing on the website approximately 3 months after the final report is published. Comments are not edited for spelling, grammar, or other content errors. Each comment is listed with the name and affiliation of the commentator if this information is provided. Commentators are not required to provide their names or affiliations in order to submit suggestions or comments.

This document includes the responses by the authors of the report to comments that were submitted for this draft report. The responses to comments in this disposition report are those of the authors, who are responsible for its contents, and do not necessarily represent the views of the Agency for Healthcare Research and Quality.

Summary of Peer Reviewer Comments and Author Response

This systematic review and meta-analysis underwent peer review before the draft report was posted for public comment. Peer reviewers' comments are summarized below.

- Reviewers evaluated the methodological quality and clinical relevance of the draft report. They found the approach and methodology of the systematic review appropriate and rigorous. Reviewers commented that the review presented "clinically important summary of the comparative effectiveness and harms of PBI [partial breast irradiation]," "provided robust support for the use of PBI," and was "meaningful" and "very well written".
- Some reviewers pointed out some additional studies about the topic that were not included and suggested additional references to be included. The Evidence-based Practice Center reviewed these references and found that none of them met the *a priori* defined inclusion criteria. Therefore, such references could not be added to the review.
- Some reviewers requested a clarification of the definition of financial toxicity. In this report, financial toxicity was defined as subjective or objective financial distress and hardship experienced by patients due to cancer-related (or anticipated) treatment. This definition included direct and indirect medical costs from patients' perspective and did not include societal costs related to PBI. The definition is clarified in the revised systematic review with additional discussion of the impact of financial burden when selecting treatments.
- One reviewer suggested changing the terminology "ipsilateral breast tumor recurrence (IBTR)" to "ipsilateral breast recurrence (IBR)" to be consistent with the Standardized Definitions for Efficacy End Points in Adjuvant Breast Cancer Clinical Trials, Version 2.0. We agree and changed IBTR to IBR throughout the report.
- Reviewers requested the addition of text that describes the direction of meta-analysis estimates in Tables 5–8. We added a dedicated column to these tables to present directions of effects (i.e., favors PBI, favors WBI, or no difference).
- One reviewer asked about the absolute treatment effect. In the revised manuscript, we added the risk difference and related 95% confidence interval to help readers understand the magnitude of the effect and judge statistical relevance along with clinical relevance of the results.

Public Comments and Author Response

Commentator & Affiliation	Section	Comment	Response
American Society for Radiation Oncology (ASTRO)	General	Global Questions: 1) The authors seemed to have compiled data on subgroups (ie; age, size, margins) but that is not provided anywhere in a collated way to examine these and see the number of patients within each of these subgroup populations particularly in the RCT. Do the authors of the AHRQ report have this information and would they be willing to share this with the ASTRO Task Force, as this would be very helpful for us in making recommendations particularly for these groups which were previously evaluated as "cautionary" on the ASTRO guidelines. In looking at the subgroup analysis tables (Appendix J) there are no references provided and so if our group wants to try to look at the primary source data from which these were derived, it would help to have references to know which manuscripts were included for each comparison. Put another way, would be great to take the data in appendix D.1, last column ("patient characteristics") and create a table that contains the #,% of patients in these categories in each trial	We added additional data as requested.
American Society for Radiation Oncology (ASTRO)	General	Global Questions: 2) Can any of the tables for which IRR, RR and HR were provided also provide information regarding gross (absolute) incidence of recurrences and toxicities? These absolute numbers and not relative numbers are oftentimes what guide patient and provider recommendations.	We added additional data as requested.
American Society for Radiation Oncology (ASTRO)	General	Global Questions: 3) ES-3 and ES-4: Please provide the raw data used to determine that insufficient evidence is present for aggregate analysis from all the studies pertaining to KQ 1 and 2. These include the absolute number of patients with the following characteristics who participated in the trials used for analysis of KQ 1 and 2: a) Age < 50 b) ILC c) Tumor size 2.1 – 3 cm d) Grade 3 e) ER Negative status f) HER2 positive status g) Positive LVI h) Elevated Ki-67 i) Extensive intraductal component (EIC) j) DCIS	We provided raw numbers (e.g., age, tumor size, tumor grade) in Appendix Table J subgroup analyses. In the results section of the full report, we summarized patients characteristics by key questions.

Commentator & Affiliation	Section	Comment	Response
American Society for Radiation Oncology (ASTRO)	General	Global Questions: 4) For the purposes of the ASTRO Guideline, please make accessible the absolute numbers and p-values for all subgroups analyses contained in Tables 5-8.	We added p value for the interaction between all subgroup analyses in Appendix J.
American Society for Radiation Oncology (ASTRO)	General	Global Questions: 5) Is cosmesis included as a late effect?	Cosmesis outcome is reported separately from late effects as defined by the Harvard Scale or EORTC scale. Table 3 demonstrates the categories of adverse events reported. While some of the items, such as the presence of fibrosis or telangiectasia may impact cosmetic result, cosmesis is a distinctly reported outcome as shown in Table 2.

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American Society for Radiation Oncology (ASTRO)	General	Global Questions: 6) Will all studies included in the analysis of KQ1 be used in the analysis of KQ2 if the key questions are combined?	When a study included comparisons between PBI modalities, in addition to the comparison between PBI and WBI, we included the study in KQ2 as well as KQ1.
American Society for Radiation Oncology (ASTRO)	General	Abstract. While it may be standard format, the use of the word “harms” when referring to PBI compared to WBI gives a negative connotation to this technique. Can risks/benefits be used instead?	We prefer to retain the original language in the protocol that is common for systematic reviews. Risk/benefit terminology may imply that we did some sort of risk benefit analysis.
American Society for Radiation Oncology (ASTRO)	General	Abstract. Why remove that IORT has a higher IBR – this was previously in the abstract and is a very salient point clinically. If this is removed, then the IBR data from other modalities should also be removed from the abstract.	Agree. The IBR results have for IORT have been added back into the abstract.
American Society for Radiation Oncology (ASTRO)	General	Abstract. Statement about “significantly fewer adverse events (AEs) with PBI compared with WBI with no apparent difference in late AEs (moderate SOE). Data about quality of life were limited.” This statement would benefit from being rephrased to “no apparent difference in late effects” and is probably a result of analyzing whole groups together. However, as we know, dose fractionation was heterogeneous, resulting in heterogeneous results. There are some fully powered trials that did show an improvement. We believe the statement needs to be nuanced.	We added a statement to the discussion detailing the heterogeneity between studies in late AE results.
American Society for Radiation Oncology (ASTRO)	General	Conclusions that PBI has lower transportation costs needs to be qualified that it depends on fractionation of PBI (accelerated vs. not) and fractionation of comparator whole breast arm.	Agree and modified.

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American Society for Radiation Oncology (ASTRO)	General	Why are statements about cosmesis with bid vs qd removed, as this is also a main, clinically relevant point. Can narrow point to cosmesis with EBRT and conclude that for all EBRT trials that reported on cosmesis (Budapest, Florence, IMPORT-LOW, RAPID), those with once daily fractionation showed better cosmesis with PBI and those with twice daily tx showed worse cosmesis with PBI (this is based on section 3.2.2.1.4).	The findings were generated from subgroup analyses and suffer higher risk of bias. The findings should be used for generating hypothesis and interpreted cautiously. In Appendix Table J.23, we added citations for each subgroup. For the cosmetic outcomes, only studies with IMRT or 3DCRT were included. In the discussion section, we describe differences in cosmetic outcomes for studies that used only external beam PBI.
American Society for Radiation Oncology (ASTRO)	General	Minor Points: ES-1 and p1 – add a reference to highest risk area of recurrence is in the tumor bed.	We added the reference.

Commentator & Affiliation	Section	Comment	Response
American Society for Radiation Oncology	General	Minor Points: ES-1 & ES-4 – the number of patients included in randomized trials is referred to as >10,000 women (ES-1) and 15,045 women (ES-4). This difference must be excluding vs including the IORT randomized trials but is not explicitly stated. In some places where broad statements are made about the effectiveness of PBI, I'm not clear if IORT patients are included or excluded. For example, right after listing the 15,045-patient number, there is a sentence stating: "In aggregate, the results… showed no difference between PBI and WBI…". Does this mean that the increased IBTR rate with IORT was small enough that it "disappeared" when those studies are pooled with the EBRT/brachy studies?	We clarified this statement that over 15,000 women have participated in clinical trials of PBI. IORT results were analyzed and reported separately from other PBI modalities throughout the manuscript. The statement about no difference between PBI and WBI refers to analysis that does not include IORT results.
American Society for Radiation Oncology (ASTRO)	General	Minor Points: Reference should be provided regarding WBI in 10 fractions (they reference 5-10 fractions – I am only familiar with a 5 fraction regimen but not 6-10 fraction). 10 fractions could refer to when you add a 5-fraction lumpectomy boost, which could be more clearly stated here.	We added references. WBI in 10 fractions refers to patients who received WBI followed by a boost, as described in the FAST-Forward clinical trial.
American Society for Radiation Oncology (ASTRO)	General	Minor Points: P.4, 2.3 – Analytic Framework – under effect modifiers, margins should be added since it was listed.	Added.

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American Society for Radiation Oncology (ASTRO)	General	Minor Points: Table 1 – refer to cosmesis and using Harvard Breast Cosmesis Scale and Global Cosmesis Scale – aren't these de facto the same?	These scales are de-facto the same 4 point scale, though some trials refer to the Global cosmesis and some refer to the Harvard Cosmesis scale. We revised the table accordingly.
American Society for Radiation Oncology (ASTRO)	General	Minor Points: Table 1 – mention sexual health but no scale in the table nor is it mentioned in the report text.	We intended to include "sexual health" in the analyses without restrictions. The included studies didn't report such information. In the methods, we stated that "we were unable to conduct other prespecified subgroup analyses".
American Society for Radiation Oncology (ASTRO)	General	Minor Points: Table 1 - PICOTS subgroup analysis – list breast size and cup size – what is the distinction between these?	We deleted cup size.

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American Society for Radiation Oncology (ASTRO)	General	Minor Points: P.28, 3.2.2 – the authors cite that the ELIOT trial authors report a high rate of IBR for "suitable" PBI candidates – can they provide what that IBR incidence is for the readers for context.	In the discussion section, we describe the results of ELIOT trial in detail, including the IBR incidence among a "very low risk" group that is even more favorable than the ASTRO suitable category.
American Society for Radiation Oncology (ASTRO)	Executive Summary	ES-3 – contrasting costs of PBI vs WBI needs to state that this is looking at standard fractionation WBI	Agree and added.
American Society for Radiation Oncology (ASTRO)	Executive Summary	Implications and Conclusions – can AHRQ provide insight on whether or not insurers would stop reimbursing for the groups defined as having less certainty as defined on ES-4	This is beyond the scope of the review.
American Society for Radiation Oncology (ASTRO)	Executive Summary	If possible, it may be good to have a "research in context" box after the abstract that describes what these results mean with today's breast RT. This could include the excellent points about standard of care whole breast dose-fractionation changing to more hypofractionated regimens, so today's "standard" comparison is different. Given that acute toxicity is strongly related to total dose, rather than dose per fraction, there may be less gains in reducing acute toxicity when comparing with hypofractioned WBRT (as discussed in the report). However, there may be more evidence of reduced late toxicity if both the same hypo fractionated regimen is compared with a reduced volume for PBI - as shown with IMPORT Low - the volume effect. Therefore, the relationship stated in the abstract - reduced acute toxicity and little change in late toxicity may in fact be reversed using today's regimens for WBRT + the same dose-fractionation in PBI. This builds on what is already in the discussion, but people are more likely to read it if it is upfront.	We followed the AHRQ publication guide. We are unable to add "Research in context" box. Additional text and contextualization will likely be provided in separate guidance from ASTRO.

Commentator & Affiliation	Section	Comment	Response
American Society for Radiation Oncology (ASTRO)	Results	•P15 (3.2.2; bullet point 4) SOE should be added for patient and provider rated cosmetic outcomes and acute AEs.	SOE is rated for the main outcomes of the systematic review following a published protocol. There are tens of subgroup analyses (such as the ones mentioned in the comment) that are not feasible to rate and their rating may be misleading because they are derived from subgroup analyses.
American Society for Radiation Oncology (ASTRO)	Results	P15 – in discussing acute AEs, some data should be provided regarding the timepoint in which these were evaluated. For example, with PBI and with IORT in particular, were AE's only evaluated on the postoperative day, or at such a short timeframe that one might have missed any acute toxicities? I presume for WBI the short-term AEs were at week 6 for most patients. If this isn't addressed here it should be added to the discussion on p38.	Acute adverse events as reported herein were defined as those occurring within three months of treatment, as reported by the studies and defined in the methods on page 10. Details regarding follow up time schedule vary depending on the study.

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American Society for Radiation Oncology (ASTRO)	Results	P16 IMPORT Low is not included as one of the trials that investigates QoL – however, this has been published and uses the same EORTC QLQ-BR23 breast and arm symptoms scores from the other trials as QOL endpoints – and has reported the constituent items from the exact same scales, albeit not the composite scores. We believe it is important that this be included.	The publication (Bhattacharya 2019, JCO) was included in the review. However, the publication only reported QoL for the whole cohort and did not report the comparison between PBI and WBI. Thus, we didn't include the results there. If there is another publication we missed in the literature search, we will add the findings.

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American Society for Radiation Oncology (ASTRO)	Results	P17 – if IBR was higher with IORT but mastectomy-free survival was not different with IORT vs WBI then how were recurrences treated after IORT? This information is clinically relevant and meaningful if the ultimate goal is breast conservation and IORT had a higher IBR.	The TARGIT-A trial reports the rates of mastectomy free survival. There was no significant difference in the rates of mastectomy despite higher risk for local recurrence. While this implies repeat breast conserving surgery was a choice for some patients, this is not explicitly reported in the data. We agree that this is clinically meaningful endpoint for patients. We have addressed this in the discussion and highlight that the convenience of therapy may be appealing despite a higher risk of IBR based on no difference detected between mastectomy rates or survival outcomes.

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American Society for Radiation Oncology (ASTRO)	Results	P 24 and P 33 contain information that I would consider “critical effectiveness outcomes” and should therefore be associated with SOEs.	SOE is rated for the main outcomes of the systematic review following a published protocol.
American Society for Radiation Oncology (ASTRO)	Results	P27 – there is a statement that there is “no significant difference in PBI effectiveness between subgroups” but on ES-4 they state that there is “uncertainty remains regarding the magnitude of increased risk” associated with these subgroup features – these seem like very different approaches. On p27 there is no mention of tumor size (2-3pm) but that subgroup is listed elsewhere as a subgroup analysis.	The comment is not clear. As we understand it, the comment is about the fact that subgroup analyses did not demonstrate significant differences but there is uncertainty about them. This is in fact is true and unfortunately additional data are needed to support inferences from subgroup analyses. The results and discussion sections describe findings of the analysis of tumor size.
American Society for Radiation Oncology (ASTRO)	Results	KQ2 – is it possible to make any conclusions or statements comparing modalities across trials or are they only allowed to look at publications that provide direct head-to-head comparisons? If only the latter, as it currently is structured, the findings for KQ2 are limited and the ASTRO Guidelines Committee will likely try in a loose way to look at cross publication comparisons.	Data are insufficient for a network meta-analysis and indirect comparisons.

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American Society for Radiation Oncology (ASTRO)	Results	P30 – 3.3.2.3 – in the discussion about protons, they list very low incidence of telangiectasias. However, in the Discussion, P39, they refer to as many as 69% of patients having telangiectasias – I do not understand why this high number is not in the results section, particularly since reference 77 is included in the results section in 3.3.2.3 – this seems to be a salient point. I also cannot find this 69% value in the Appendix which provides detailed information about toxicities.	The results section includes late toxicity, which encompasses the telangiectasia result. We added a line highlighting the increase in late toxicity result. No other individual late toxicity is reported within the tables; however the increased RR of telangiectasia is reported in table I2 of the appendix, which we now referenced in the results. We clarified that the 69% is “any telangiectasia” as reported in the study.

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American Society for Radiation Oncology (ASTRO)	Results	P.33 Table 8 KQ2 – why is strength of evidence not listed in this table? Given that findings from the discussion address some of the comparisons between PBI modalities from this table (ie; acute toxicities being lower with IMRT and single entry brachy) it would help if the SOE were on this table to know how robust a finding this is – for example, if only 1 observational study of 104 patients favored IMRT to 3DCRT I do not know that i would put that in the discussion as a takeaway point.	SOE is rated for the main outcomes of the systematic review following a published protocol. There are tens of estimates for other outcomes or from subgroup analyses that are not feasible to rate and may very well all fall in the insufficient category. We added discussion about the significant limitations of the data comparing PBI modalities.

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American Society for Radiation Oncology (ASTRO)	Results	Page 41: Section 3.2.2.7, separates out dose/fractionation for PBI into 3 categories: twice daily in 10fx, 5 treatments to 30Gy and nonaccelerated PBI. May be nice to look at cosmesis using these dose/fractionation categories.	We conducted these subgroup analyses based on available data reported by the studies, reported in table J.23. In the report, we describe comparison of twice daily treatment in 10 fractions compared to 5 treatments every other day. Due to limitations in the available data, we were unable to make a comparison of nonaccelerated PBI.
American Society for Radiation Oncology (ASTRO)	Results	Section 3.4.2 should state in body of text the fractionation schemes used in the APBI and WBI arms as this is directly relevant to findings and will allow reader to understand generalizability of findings.	Agree and added.
American Society for Radiation Oncology (ASTRO)	Discussion	For financial toxicity should mention WBI as standard fractionation.	Added.
American Society for Radiation Oncology (ASTRO)	Discussion	4.3.1 – the authors state that clinicians can consider treating with 26Gy in 5 fractions using mini-tangents for larger tumors. This dose fractionation regimen was NOT studied in any of the level I evidence evaluating PBI and it does not seem appropriate for this to be a suggestion from AHRQ – while it may be reasonable clinically, it is an extrapolation from the FAST-Forward data and seems to be a more nuanced clinical interpretation than something with firm data to support the practice. In contrast, in the UK, where much of the data on PBI and ultrahypofractionated WBI has been compiled in RCT, larger PBI volumes are considered acceptable, and toxicity is thought to be low and more dependent on dose fractionation.	The reference to the use of 26 Gy in 5 fractions has been removed and the reference to mini-tangents cites the IMPORT LOW trial.
American Society for Radiation Oncology (ASTRO)	Discussion	4.3 – there is a lot of good information here about subgroups, such as size, age, hormone receptor status, margin, etc; and it would help to have this broken out, as the details of how many patients within each age subgroup, triple negative subgroup, etc; were on the RCT	We added the data as requested.

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American Society for Radiation Oncology (ASTRO)	Discussion	P.42 – "widespread use of daily imaging with higher resolution" is not something that, to our knowledge, is documented and not necessarily something that is widespread (but does of course reimburse at a higher rate).	We modified this statement to remove the words higher resolution from the sentence. Please see below: *We found that most of the included studies required portal imaging for treatment setup verification, which was routine practice at the time the clinical trials were designed but is not reflective of current practice, with widespread use of daily imaging, similar to the approach described by Franceschini et al.*[40]

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American Society for Radiation Oncology (ASTRO)	Discussion	P. 42 I again do not know of any published data regarding the 1cm PTV margin being "markedly larger than contemporary practice when daily image guidance is used". These 2 bullet points may make more sense in a section under future directions.	We modified this statement to remove the word markedly from the sentence. Please see below: *Additionally, most of the randomized trials included in our analysis used a 1 cm expansion to create the planning target volume (PTV), which is larger than contemporary practice when daily image guidance is used.*
American Society for Radiation Oncology (ASTRO)	Discussion	P. 42. Section 4.3.8: "The use of a tumor bed boost is associated with lower risk for IBR for some women with breast cancer; however, it is also associated with an increased risk for AEs, including late AEs with fibrosis. Conventionally fractionated WBI has largely been supplanted by hypofractionation completed over approximately 3 weeks, which is associated with lower risk for AEs." Consider rephrasing this, as 2Gy daily fractions are really no longer "conventional"	We added description of 2 Gy daily fractions when discussing WBI regimens.
American Society for Radiation Oncology (ASTRO)	Discussion	P. 46-47. Discussion: It would be worth mentioning that the UK RCR breast consensus now state 26Gy in 5F can be offered or PBI and the ESTRO-ACROP consensus (published in Lancet Oncology) is also in line with this. This should be addressed in the discussion.	We added a reference to both guidelines and include discussion of 26 Gy in 5 fractions as an acceptable PBI regimen.

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American Society for Radiation Oncology (ASTRO)	Discussion	Section 4.3.4, “lymph nodes status (424 patients). Pls clarify if this number is including ITCs, micromets, and/or macromets. Would be nice to break down by these 3 categories.	The available data are not sufficiently detailed to be able to report these 3 categories.
American Society for Radiation Oncology (ASTRO)	Discussion	May be nice to add subsections to section 4.3 on LVI and EIC, two factors that make patients cautionary according to previous ASTRO APBI guidelines.	We added a statement regarding insufficient data for evaluation of EIC. The limited data available for LVI is described in the results section and table J.13.
American Society for Radiation Oncology (ASTRO)	Discussion	Maybe not so critical if dose/fractionation is optimised? E.g. large PBI volume in IMPORT Low showed decreased toxicity compared with a hypofractionated WBRT control that is gentler on the normal tissues - 40Gy in 15F over 3 weeks	We added a statement describing use of larger treatment volumes when WBI dose regimens are used and describe the lower toxicity with PBI on the IMPORT-LOW study.

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American Society for Radiation Oncology (ASTRO)	Discussion	P. 47. Conclusion: “PBI is associated with fewer acute adverse effects and less financial toxicity than WBI.” This is compared to “traditional” dose/fractionated RT over ~6 weeks, a point which needs to be highlighted.	The fractionation information has been added to the financial toxicity section, and we added conventionally fractionated to the statement about financial toxicity in the conclusions
American Society for Radiation Oncology (ASTRO)	Discussion	It may be worth adding somewhere that no RT may be an option for patients at very low risk of recurrence (with all the caveats of risk & benefit & patient preference discussed). This is supported by the LUMINA results and other biomarker-directed trials are ongoing/in follow up. In case a section on de-escalation (optimization) of treatment is added (i.e., RT omission following the single arm LUMINA data), please provide the evidence to de-escalate also systemic treatment rather than local treatment for ultra-low risk breast cancer, highlighting the potential toxicity added by e.g. endocrine therapy. A phase 3 trial is ongoing, comparing excusive PBI vs exclusive ET for luminal A-like T1N0 patients, with co-primary endpoints local relapse and health-related quality of life (Meattini I, Poortmans PMP, Marrazzo L, Desideri I, Brain E, Hamaker M, Lambertini M, Miccinesi G, Russell N, Saieva C, Strnad V, Visani L, Kaidar-Person O, Livi L. Exclusive endocrine therapy or partial breast irradiation for women aged ≥70 years with luminal A-like early stage breast cancer (NCT04134598 - EUROPA): Proof of concept of a randomized controlled trial comparing health related quality of life by patient reported outcome measures. J Geriatr Oncol. 2021 Mar;12(2):182-189. doi: 10.1016/j.jgo.2020.07.013. Epub 2020 Jul 29. PMID: 32739355).	We referenced the DEBRA trial and this concept in the discussion. We have expanded this section and named the DEBRA trial, as well as added the LUMINA trial early results.
American Society for Radiation Oncology (ASTRO	Appendix	Appendix: Appendix L – ASTRO Studies – are these studies that only examined “suitable” patients per ASTRO criteria, or they evaluated outcomes based on ASTRO stratification? It is not clear reading the primary report nor the appendix what this represents	These studies are provided by ASTRO for additional references. We revised the heading to clarify this.

Commentator & Affiliation	Section	Comment	Response
Benjamin Smith, MD, MD Anderson Cancer Center	General	I would like to see some mention of single entry catheter brachytherapy in the Main points, even if just to say that there is insufficient evidence to determine if outcomes with this approach are different than other PBI approaches. In Implications and Conclusions, it is stated that further investigation is needed to define optimal radiation treatment technique for PBI. To technique, I would add dose as well. The twice daily dosing regimen seems to cause excess toxicity and we need more data about short, daily courses of PBI other than the trial from University of Florence, in my opinion. This is a very well-written report and I am impressed with the authors' depth of knowledge on this topic. Thank you very much!	In the main points section, we report, "Head-to-head comparisons between the different PBI modalities showed insufficient evidence to estimate an effect on main outcomes." We modified the implications and conclusions section to specify that evaluating the optimal dose is a key area for future study.
Diana Zuckerman, PhD, National Center for Health Research	General	We are writing to express our views on the AHRQ Draft Comparative Effectiveness Review comparing Partial Breast Irradiation (PBI) to Whole Breast Irradiation (WBI) as a treatment for early-stage breast cancer. The National Center for Health Research (NCHR) is a nonprofit think tank that conducts, analyzes, and scrutinizes research on a range of health issues, with a particular focus on which prevention strategies and treatments are most effective for which patients and consumers. We do not accept funding from companies that make products that are the subject of our work, so we have no conflicts of interest.	We appreciate the comments.

Commentator & Affiliation	Section	Comment	Response
Diana Zuckerman, PhD, National Center for Health Research	General (continued)	We agree with the AHRQ review that clinical trials provide sufficient evidence that PBI is a valuable treatment option for select patients with early-stage breast cancer. Patient outcomes for several types of PBI did not differ significantly from WBI patients in terms of ipsilateral breast recurrence (IBR), overall survival, and cancer-free survival at 5 and 10 years. However, IORT PBI patients did have higher levels of recurrence (IBR) than WBI patients, despite no difference in overall survival or cancer-free survival. Overall, PBI patients have fewer acute adverse effects, lower transportation costs and days away from work, and fewer financial strains, making it a more convenient therapy option compared to WBI. However, there are numerous types of PBI, and the data are not adequate on the effectiveness of each one of them compared to WBI. In addition, we agree with the AHRQ review that there is currently insufficient data to draw conclusions about the risks and benefits of different types of PBI compared to each other or to WBI for women who are diverse in terms of patient, tumor and treatment characteristics. Outcomes at 15 and 20 years are also important to evaluate. For these reasons, more research is necessary to provide the most useful information to patients considering breast irradiation.	We appreciate the comments.