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Review

Effectiveness of different accelerated partial breast irradiation techniques for the treatment of breast cancer patients: Systematic review using indirect comparisons of randomized clinical trials

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ABSTRACT

Aim: This systematic review was conducted to compare the effectiveness of different accelerated partial breast irradiation (APBI) techniques for the treatment of breast cancer patients.

Background: Numerous (APBI) techniques are available for clinical practice.

Methods and materials: Systematic review of randomized controlled trials of APBI versus whole breast irradiation (WBI). The data from APBI studies were extracted for the analyses. Indirect comparisons were used to compare different APBI techniques.

Results: Ten studies fulfilled the inclusion criteria. A total of 4343 patients were included, most of them with tumor stage T1-T2 and N0. Regarding APBI techniques, six trials used external beam radiation therapy; one intraoperative

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electrons; one intraoperative low-energy photons; one brachytherapy; and one external beam radiation therapy or brachytherapy. The indirect comparisons related to 5-years local control and 5-years overall survival were not significantly different between APBI techniques.

Conclusions: Based on indirect comparisons, no differences in clinical outcomes were observed among diverse APBI techniques in published clinical trials that formally compared WBI to APBI. However wide confidence intervals and high risk of inconsistency precluded a sound conclusion. Further head-to-head clinical trials comparing different APBI techniques are required to confirm our findings. Studies comparing different techniques using individual participant data and/or real-life data from population-based studies/registries could also provide more robust results.

1. Backgroud / Aim

Over the last 30 years, breast-conserving therapy (BCT) has been accepted as a standard-of-care practice for early stage breast cancer patients.[1] Based on phase III randomized studies, when compared to radical mastectomy alone, breast-conserving surgery followed by whole breast irradiation (WBI) is associated with at least equivalent overall survival and local regional recurrence rates.[2–8]

However, conventionally fractionated WBI comprises 25–33 daily fractions of treatment, reduced to 15–21 days using a hypofractionated schedule.[9] Due to the duration of this WBI course and other issues, such as the limited capacity of radiation therapy (RT) services, a considerable number of patients eligible for BCT management undergo mastectomy or breast-conserving surgery without RT.[10–12]

It is recognized that the most frequent region of local tumor recurrence is the surgical bed in patients with early stage breast cancer. Therefore, the main benefits of postoperative RT are related to the treatment delivered around the tumor cavity.[13,14] For this reason, accelerated partial breast irradiation (APBI), where treatment is performed only in a restricted area of breast tissue surrounding the tumor bed, is now considered as an alternative to WBI. The most important benefit of the APBI is that this modality can be delivered after BCT over a shorter period of time (1 week or less), optimizing the logistical feasibility of radiation treatment.

While individual studies have shown the efficacy of APBI with regard to clinical outcomes,[15–17] a meta-analysis of randomized phase III trials demonstrated that APBI is associated with a higher risk of local relapse.[18]

Numerous APBI techniques are available for clinical practice, such as brachytherapy, external-beam RT and intraoperative RT (IORT) with low-energy photons or electrons.[19] It remains uncertain whether these distinct modalities result in the same or different clinical outcomes. Hence, this systematic review was conducted to evaluate the effectiveness of different APBI techniques for the treatment of breast cancer patients.

2. Material and methods

2.1. Design

A systematic review using indirect comparisons was planned and conducted as preview described.[20] Indirect comparisons were used because no head-to-head comparisons of different APBI techniques were reported by any of the studies included in this review. When no head-to-head comparisons are available, an indirect comparison compares two interventions using information from studies comparing one of the interventions of interest with a third, common comparator.[21] For reporting the results, we followed the recommendations of the PRISMA Statement for network-meta-analysis.[22]

2.2. Criteria for considering studies for this review

(a) Types of studies: Randomized clinical trials (RCTs), regardless of publication status (published as full-text or abstract).
(b) Types of participants: Breast cancer patients.
(c) Types of interventions: Any technique of partial breast irradiation, regardless of the therapeutic co-intervention (surgery, chemotherapy, target or immune therapy).

2.3. Outcomes

The primary outcome was the time to local recurrence and the secondary outcome was overall survival.

2.4. Search methods for identification of studies

We searched the electronic databases Central Register of Controlled Trials (CENTRAL, 2017 issue 7, via Wiley), MEDLINE (1966 to 25 March 2017, via Pubmed), and EMBASE (1988 to 25 March 2017, via Elsevier). We contacted experts on the topic looking for published and unpublished studies. For ongoing trials, we searched Clinicaltrials.gov and WHO International Clinical Trials Registry Platform (ICTRP) (March 2017).

Manual searches were done by assessing the reference lists of included studies and review articles for references. No restriction regarding language, date or status of publication was applied. The search strategy for each database is presented in Supplementary material 1. All studies that reported local recurrence and overall survival rates were included.

2.5. Selection of studies and assessment of the risk of bias

Two reviewers independently selected and assessed the risk of bias of the included trials in accordance with the Handbook for Systematic Reviews of Interventions.[23] Disagreements were resolved by a third reviewer.

2.6. Data extraction and analysis

Two review authors extracted information from studies and completed a standard form with methodological characteristics and outcome data from included studies. One review author transcribed the data from the form into Stata version 14. We double-checked that the data were properly entered by comparing with the original study report.

2.7. Statistical analysis

To estimate the effect size, we assessed time-to-event data as hazard ratios (HR), assuming a 95% confidence interval (CI). When HRs were not available we endeavored to estimate them from reported results using the methods of Parmar et al.[23] To allow for the possibility of non-proportional hazards, HRs were estimated using 5-year survival data for all studies. Indirect comparisons were estimated using the methods of Bucher et al.[21]

Findings were reported using a league table to display direct and indirect comparisons.[24]

2.8. Assessment of heterogeneity and inconsistency

(a) Statistical heterogeneity: For the direct comparisons with WBI we used the I^2 statistic to quantify heterogeneity between studies.[25]
(b) Statistical inconsistency: No formal test for inconsistency could be conducted because there were no direct comparisons. We compared baseline characteristics and local recurrence in the WBI group between studies used for indirect comparisons.[26]

3. Results

3.1. Study selection and features of the included trials

Ten studies[27–37] retrieved fulfilled the inclusion criteria for this review (Table 1). The flowchart with the process of the studies selection is detailed in Supplementary material 2. A total of 4343 patients were included, most of them with tumor stage T1-T2 and N0 (Table 2). The analyses were performed based on six trials[27,28,34–37] that reported local recurrence and overall survival outcomes.

Regarding APBI techniques, six trials used external beam RT[27–29,32,37]; one intraoperative electrons[34]; one intraoperative low-energy photons[35]; one brachytherapy[36]; and one external beam RT or brachytherapy.[30,31] Data from the Polgar study[30,31] was not considered for analyses because individual information about clinical outcomes for patients who received conventionally fractionated APBI with external beam electrons or APBI with brachytherapy was not available.

3.2. Methodological quality of studies

The methodological quality of the included studies is shown in Supplementary – Materials 3. Overall, all the ten studies were classified as high risk of bias taking into account the lack of blinding of patients and/or outcome assessors. However, except for this item (blinding), ten studies were considered as high quality and low risk of bias.

3.3. Consistency

There are no direct comparisons across included trials regarding APBI techniques; thus, we assess for inconsistency by comparing baseline characteristics (Table 1) of all studies. Direct comparisons for APBI versus WBI are presented in Supplementary – Materials 4 and 5. Of the six studies contributing data to analyses, four reported the mean age of patients. The mean age of patients in the Dodwell[27] study was lower than the mean age of patients in the Coles,[37] Strnad[36] and Vaidya[35] studies. Regarding tumor stage, most patients had tumor stages T1-T2 in all contributing studies (range 89% to 100%) and no patients were included with tumor stages T3-T4. The proportion of patients with estrogen receptor (ER) positive status was similar in the five contributing studies that reported it (range 68.9% to 95%). The proportion of patients receiving adjuvant chemotherapy was low in most studies, except the Dodwell[27] study in which all patients received chemotherapy.

Despite some differences in patient selection criteria and adjuvant treatment protocols of included trials, local control rates in the WBI groups were similar, demonstrating that it might be a way to control for selection differences.[27,28,34–37]

3.4. Local control

Indirect comparisons related to local control at 5 years were observed in Table 2 and Fig. 1. Six studies comprising 6758 patients were included.[27,28,32,34,36–38] There were no statistically significant differences in 5-year local recurrence between APBI techniques, but all results had wide confidence intervals and the risk of inconsistency is high because there was no available information from direct comparisons. Further research is therefore required to draw any firm conclusions.

3.5. Overall survival

Six studies comprising 6758 patients were included in analyses of overall survival.[27,28,32,34,36–38] No statistically significant differences between APBI techniques for 5-year overall survival were found based on indirect comparisons. But again, the confidence intervals were too wide and the risk of

Table 1 – Characteristics of included studies.

Study	Patients	Mean age			Inclusion criteria	Tumor stage, *n* (%)		Nodal stage, *n* (%)				Grade, *n* (%)			Estrogen receptor and HER-2 status		APBI	Che, *n* (%)	HT, *n* (%)
	APBI arm (*n*)	WBI arm (*n*)	APBI arm (*n*)	WBI arm (*n*)		*Tis*	*T1–T2*	*N0*	*N1 - N2*	*N3*	*No data*	*I - II*	*III*	*No data*	ER positive, *n* (%)	HER-2 positive, *n* (%)			
Dodwell[27] (2005)	84	90	52	51.5	pT1-2 pN0-1	0 (0%)	174 (100%)	111 (63.8%)	63 (36.2%)	0 (0%)	0 (0%)	127 (72.9%)	47 (27.1%)	0 (0%)	–	–	External beam radiation therapy: 55 Gy/20 fx	174 (100%)	174 (100%)
Livi[28] (2015)	260	260	–	–	>40 years; T ≤ 2.5 cm; unifocal tumor; no EIC	55 (10.6%)	465 (89.4%)	445 (85.6%)	52 (10.0%)	0 (0%)	23 (4.4%)	461 (88.6%)	59 (11.4%)	0 (0%)	497 (95.6%)	19 (3.6%)	External beam radiation therapy: 30 Gy/6 fx	35 (6.7%)	317 (60.9%)
Olivotto[29] (2013)	1070	1065	–		≥40 years; DCIS; IDC ≤ 3 cm; pN0	366 (17.2%)	1752 (82.0%)	2135 (100%)	0 (0%)	0 (0%)	0 (0%)	1425 (66.7%)	302 (14.2%)	25 (1.1%)	1471 (68.9%)	–	External beam radiation therapy: 38.5 Gy/10 fx twice daily	267 (12.5%)	1186 (55.5%)
Polgar[31] (2013)	128	130	59	58	Unifocal tumor; ≤ pT2; cN0, pN0, or pN1mi (single nodal >0.2 mm and ≤ 2 mm); histologic grade ≤ 2	0 (0%)	258 (100%)	244 (94.6%)	9 (3.4%)	0 (0%)	5 (2.0%)	258 (100%)	0 (0%)	0 (0%)	229 (88.7%)	–	HDR MI: 36.4 Gy/7 fx or external beam radiation therapy: 42–50 Gy/21–25 fx	7 (2.7%)	207 (80.2%)
Ribeiro[32] (1993)	353	355	53	52	<70 years; tumor ≤4 cm; cN0	0 (0%)	708 (100%)	–	–	–	–	–	–	–	–	–	External beam radiation therapy: 40–42.5 Gy/8 fx	0 (0%)	0 (0%)
Rodriguez[33] (2013)	51	51	67.1	70.1	≥60 years; IDC; unifocal tumor; ≤pT2; cN0 (pN0 axillary status); histologic grade ≤2	0 (0%)	102 (100%)	102	0 (0%)	0 (0%)	0 (0%)	102 (100%)	0 (0%)	0 (0%)	100 (98.0%)	1 (0.9%)	External beam radiation therapy: 37.5 Gy/10fx twice daily	3 (2.9%)	101 (99.0%)
Veronesi[34] (2013)	651	654	–	–	48–75 years; tumor <2.5 cm	0 (0%)	1305 (100%)	949 (72.7%)	276 (21.2%)	69 (6.1%)	–	990 (75.8%)	274 (20.9%)	32 (3.3%)	1172 (89.8%)	44 (3.3%)	Intraoperative electrons – 21 Gy/1fx	100 (7.6%)	1154 (88.4%)

– Table 1 (*Continued*)

Study	Patients	Mean age			Inclusion criteria	Tumor stage, *n* (%)		Nodal stage, *n* (%)				Grade, *n* (%)			Estrogen receptor and HER-2 status		APBI	Che, *n* (%)	HT, *n* (%)
	APBI arm (*n*)	WBI arm (*n*)	APBI arm (*n*)	WBI arm (*n*)		*Tis*	*T1–T2*	*N0*	*N1 - N2*	*N3*	*No data*	*I - II*	*III*	*No data*	ER positive, *n* (%)	HER-2 positive, *n* (%)			
Vaidya[35] (2010)	1113	1119	63	63	≥45 years; IDC; T1-T2; unifocal tumor; no EIC	0 (0%)	2232 (100%)	1764 (79.0%)	304 (13.6%)	61 (2.7%)	100 (4.7%)	1769 (79.2%)	319 (14.2%)	144 (6.6%)	1943 (87.0%)	264 (11.8%)	IntraBeam – 20 Gy (surface of the tumor bed)/5–7 Gy at 1 cm depth	257 (11.5%)	1480 (66.3%)
Strnad[36] (2016)	633	551	62	62	≥40 years; pTis or pT1–2a (lesions of ≤3 cm diameter), pN0/pNmi	60 (5.1%)	1124 (94.9%)	1123 (94.8%)	10 (0.08%)	0 (0%)	51 (5.1%)	1072 (90.5%)	99 (8.3%)	13 (1.2%)	1082 (91.4%)	–	HDR MI (32 Gy in 8 fractions or 30.3 Gy in 7 fractions, with fractionation twice a day,) or PDR (50 Gy with pulses of 0.60–0.80 Gy/h)	128 (10.8%)	1031 (87.0%)
Coles[37] (2017)	669	674	62	62	≥50 years; unifocal tumor; pT1–2; pN0-1	0 (0%)	1343 (100%)	1303 (97.0%)	40 (3.0%)	0 (0%)	0 (0%)	1212 (90.3%)	127 (9.7%)	0 (0%)	1273 (94.8%)	57 (4.2%)	External beam radiation therapy: (40 Gy/15 fx)	62 (4.6%)	1212 (90.2%)

Notes: * Hormonal receptors positive; APBI, accelerated partial breast irradiation; Che, adjuvant therapy with chemotherapy; DCIS, ductal carcinoma in situ; EIC, extensive intraductal carcinoma; ER, estrogen receptors; HDR MI, high-dose-rate multicatheter interstitial; HT, adjuvant therapy with hormone; IDC, invasive ductal carcinoma; IMRT, intensity-modulated radiotherapy; PDR, pulsed-dose-rate; Fx, fractions.

Table 2 – Local recurrence at 5 years. Tables showing B versus A hazard ratios and 95% confidence intervals. The upper half-triangle of the table shows results from direct comparisons and the lower half-triangle shows results from indirect comparisons. An empty cell indicates no evidence of that type.

		B				
		WBI	EBRT	BT	IB	IOE
A	WBI		1.15 (0.57, 2.31)	1.63 (0.57, 4.66)	3.07 (1.83, 5.18)	4.69 (1.99, 11.03)
	EBRT					
	BT		0.70 (0.20, 2.48)			
	IB		0.37 (0.16, 0.89)	0.53 (0.16, 1.71)		
	IOE		0.25 (0.08, 0.74)	0.35 (0.09, 1.35)	0.66 (0.24, 1.79)	

Note: WBI, whole breast irradiation; EBRT, external beam radiation therapy; BT, brachytherapy; IB, intraoperative low energy photons (IntraBeam); IOE, intraoperative electrons.

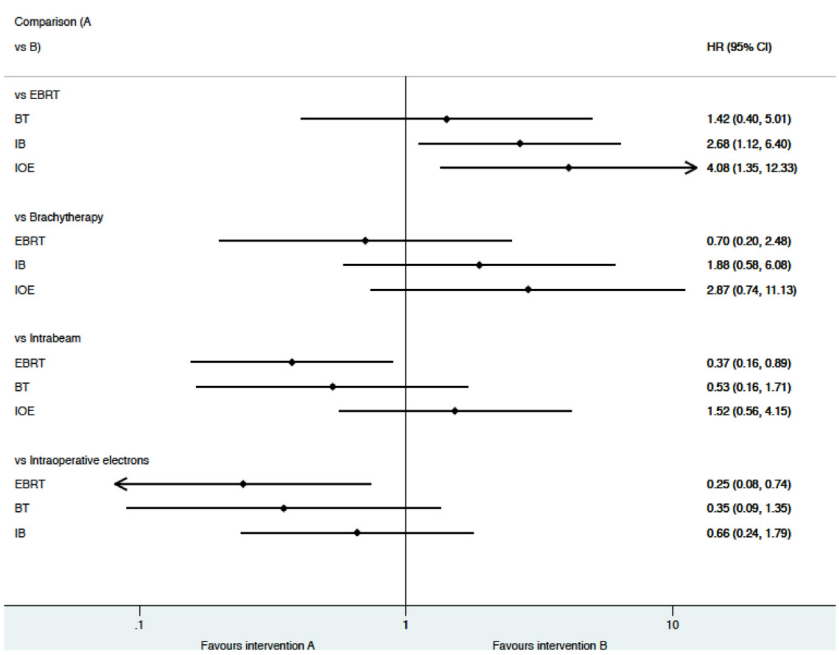

Fig. 1 – Indirect comparisons related to local control at 5 years. Note: EBRT: external beam radiation therapy; BT: brachytherapy; IB: intraoperative low energy photons (IntraBeam); IOE: intraoperative electrons.

Table 3 – Overall survival at 5 years. Tables showing B versus A hazard ratios and 95% confidence intervals. The upper half-triangle of the table shows results from direct comparisons and the lower half-triangle shows results from indirect comparisons. An empty cell indicates no evidence of that type.

		B				
		WBI	EBRT	BT	IB	IOE
A	WBI		0.84 (0.59, 1.19)	0.58 (0.31, 1.07)	0.75 (0.55, 1.02)	1.00 (0.53, 1.89)
	EBRT					
	BT		1.45 (0.72, 2.96)			
	IB		1.12 (0.70, 1.78)	0.77 (0.39, 1.53)		
	IOE		0.84 (0.41, 1.73)	0.58 (0.24, 1.40)	0.75 (0.37, 1.52)	

Note: WBI, whole breast irradiation; EBRT, external beam radiation therapy; BT, brachytherapy; IB, intraoperative low energy photons (IntraBeam); IOE, intraoperative electrons.

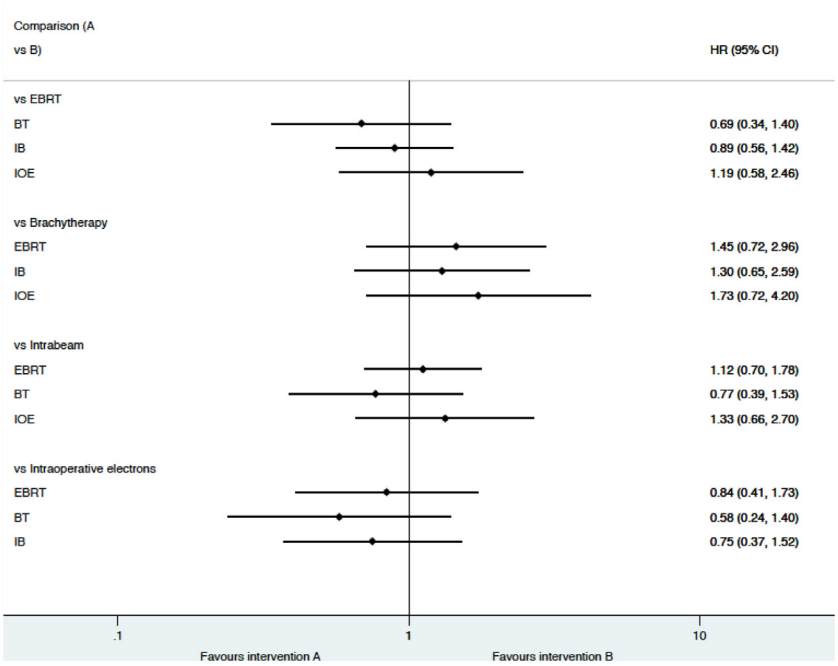

Fig. 2 – Indirect comparisons related to overall survival at 5 years. Note: EBRT: external beam radiation therapy; BT: brachytherapy; IB: intraoperative low energy photons (IntraBeam); IOE: intraoperative electrons.

inconsistency too high to draw any reliable conclusions (Table 3 and Fig. 2).

4. Discussion

The safety and efficacy of APBI has been assessed in clinical trials using diverse techniques.[18] The outcomes of these clinical trials showed conflicting results associated with ipsilateral breast cancer event rates,[39] while confirming comparable overall survival between APBI and WBI.[34,36,38]

The use of various technical approaches to deliver APBI is known to be very physician-dependent and to influence the definition of the treated volume (the target volume should not depend on the technique).[40] Depending on the selected technique, the required technical skills vary considerably.[17,41]

In the Ribeiro et al. trial, patients were treated by means of electrons (energy of 8–14 MeV) to a prescribed dose of 40–42.50 Gy in eight fractions over 10 days. Average field size was 8 cm × 6 cm.[32]

Dodwell et al. used diversity of external beam RT techniques (electrons, direct cobalt or cesium beam or a tangential pair of MV photons). For the tumor bed definition, preoperative clinical information, patient recollection and scar location were used. There was no definition for appropriate margins and the prescribed dose was 20 fractions of 2.75 Gy.[27]

Polgar et al. used total dose of 7 × 5.2 Gy twice per day interstitial brachytherapy (HDR multicatheter – 192Ir). The protocol also permitted 50 Gy (conventional fractionation – 2 Gy/day, 5 fractions/week) of external beam RT (electron beam of 6–15 MeV). The planning target volume (PTV) was demarcated as the tumor bed (defined by the surgical clips) plus a margin of 2 cm. A smaller margin of 1–1.5 cm was used when the tumor bed was adjacent to the chest wall or skin surface.[30,31]

The ELIOT study used electrons of 4–12 MeV to deliver an intraoperative single dose of 21 Gy to the 90% isodose 1–3 cm around the tumor bed (sutured surgical breech).[34]

The TARGIT trial used 20 Gy single-dose intraoperative low energy photons of 50 kV maximum beyond the surface of a 1.5–5.0 cm applicator located in the surgical excision cavity.[35,38]

The European Brachytherapy Breast Cancer Working Group Trial used brachytherapy (high dose rate – HDR or pulsed dose rate – PDR). Three different prescription doses were authorized: 50 Gy in hourly fractions of 0.60–0.80 Gy for PDR; 30.3 Gy in 7 fractions or 32 Gy in 8 fractions, both twice a day with HDR. The PTV was defined as the surgical cavity plus a 2–3 cm geometric margin.[36,42]

The RAPID trial used external beam RT (3–5 conformal fields) to deliver a total dose of 38.5 Gy in ten fractions treated twice daily (10 × 3.85 Gy). The clinical target volume (CTV) was defined by the surgical cavity (including the surgical clips) plus a 1 cm margin inside breast tissue. The PTV was created with an extra geometric margin of 1 cm.[29]

In the Florence trial, patients were treated with intensity-modulated radiotherapy (IMRT). The CTV was created by 1 cm geometric margin around the surgical clips (tumor bed). A second margin of 1 cm was added to CTV to obtain PTV. A dose of 30 Gy in five non-consecutive daily fractions (6 Gy/fraction) was used.[28]

The prescription dose in the Rodríguez et al. trial was 37.5 Gy in 3.75 Gy/fraction delivered twice-daily using external beam RT. The PTV was demarcated by including the same quadrant as the primary tumor site (surgical clips were not used).[33]

Coles et al. used field-in-field IMRT with total dose of 40 Gy in 15 fractions. Gold seeds were sutured at the level of the tumor bed and the volume was defined by the area around the seeds and changes in the adjacent breast tissue. Over this volume, a margin of 1.5 cm was used to create CTV. The PTV was created adding 1.0 cm from CTV.[37]

Therefore, there are numerous uncertainties about the radiobiological aspects of APBI, as they include a large variability in terms of dose prescription, dose fractionation and geometry (particularly important with brachytherapy and intra-cavity approaches). Some APBI techniques, like brachytherapy, may benefit from inhomogeneous dose delivery with a hypothetical influence on the clinical outcomes. Although they have not been officially compared one against another in prospective randomized phase III trials, the results of these modalities to date seem comparable, independent of the APBI technique that was used.

In this indirect comparisons meta-analysis, we compared the results of different APBI techniques to assess the potential influence of the APBI methods on the local control and overall survival rates. Only indirect comparisons were possible due to the lack of studies investigating direct comparisons between different APBI techniques. The outcomes were analyzed based on the main APBI technique used (external beam RT, intraoperative electrons, intraoperative low-energy photons or brachytherapy). The indirect comparisons of local control and overall survival were not statistically significantly different between APBI groups, suggesting that the APBI technique may not be a principal factor of clinical outcomes in appropriately selected patients. However, it is important to point out that these findings were accompanied by wide confidence intervals and limitations inherent to indirect comparisons. Moreover, the high risk of inconsistency between studies cannot be ignored.

Due to the variety of evaluation methods with different endpoints in the included studies, no statistical analysis could be performed regarding toxicity and cosmetic outcomes. Overall, the rate of APBI severe toxicity was very low (<3%).[27–37]

Additionally, it is important to recognize that this systematic review was based on available published trials that formally compared WBI to APBI over several decades and with varying APBI techniques and patient selection. Analogous comparisons were previously performed by other authors.[18,43,44] Moreover, the main recommendations for APBI from the Groupe Européen de Curiethérapie-European Society for Therapeutic Radiology and Oncology (GEC-ESTRO) and American Society for Radiation Oncology (ASTRO) focused on patients' selection criteria regardless of APBI technique.[45,46] Thus, even taking into account its methodological limitations, our study represents the best available evidence on the issue so far, and, although we are unable to draw any definitive conclusions, this review is crucial in highlighting the need for further research in this area.

Notwithstanding the methodological quality of included studies in this indirect comparisons meta-analysis, most of them were classified as having a high risk of bias due to the lack of blinding of patients and/or outcome assessors. Nevertheless, it must be considered that in this kind of intervention, masking is not possible. In addition, it is improbable that objective outcomes might be prejudiced by the lack of blinding.

5. Conclusion

In conclusion, despite no clear differences in local control and overall survival in indirect comparisons of diverse APBI techniques in published clinical trials that formally compared WBI to APBI, we did not have enough data to draw any sound conclusions. Further head-to-head clinical trials comparing the different APBI techniques are ideally required to determine if any differences in effectiveness exist. Alternatively, studies comparing different techniques using individual data from a larger number of clinical trials and/or real-life data from population-based studies/registries might be a more appropriate solution to compare the different APBI techniques.

Conflict of interest

None declared.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at https://doi.org/10.1016/j.rpor.2019.01.009.

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