Radiotherapy and Oncology 94 (2010) 264–273

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

GEC-ESTRO Recommendations

Patient selection for accelerated partial-breast irradiation (APBI) after breast-conserving surgery: Recommendations of the Groupe Européen de Curiethérapie-European Society for Therapeutic Radiology and Oncology (GEC-ESTRO) breast cancer working group based on clinical evidence (2009)

Csaba Polgár [a,*], Erik Van Limbergen [b], Richard Pötter [c], György Kovács [d], Alfredo Polo [e], Jaroslaw Lyczek [f], Guido Hildebrandt [g], Peter Niehoff [h], Jose Luis Guinot [i], Ferran Guedea [j], Bengt Johansson [k], Oliver J. Ott [l], Tibor Major [a], Vratislav Strnad [l], On behalf of the GEC-ESTRO breast cancer working group

[a] Department of Radiotherapy, National Institute of Oncology, Budapest, Hungary; [b] Department of Radiation Oncology, University Hospital Gasthuisberg, Leuven, Belgium; [c] Department of Radiotherapy and Radiobiology, University Hospital AKH Vienna, Vienna, Austria; [d] University of Lübeck, Interdisciplinary Brachytherapy Unit, Lübeck, Germany; [e] Department of Radiation Oncology, Ramon y Cajal University Hospital, Madrid, Spain; [f] Department of Brachytherapy, Institute Marie Skodlowska-Curie, Center of Oncology, Warsaw, Poland; [g] Department of Radiation Oncology, University Hospital Rostock, Rostock, Germany; [h] University Hospital S-H, Klinik für Strahlentherapie (Radioonkologie), Kiel, Germany; [i] Department of Radiation Oncology, Fundacion Instituto Valenciano de Oncologia, Valencia, Spain; [j] Department of Radiation Oncology, Institut Catalá d' Oncologia, Barcelona, Spain; [k] Department of Oncology, Örebro University Hospital, Örebro, Sweden; [l] Department of Radiation Oncology, University Hospital Erlangen, Erlangen, Germany

ARTICLE INFO

Article history:
Received 8 October 2009
Received in revised form 4 January 2010
Accepted 23 January 2010
Available online 22 February 2010

Keywords:
Accelerated partial breast irradiation
Patient selection
Brachytherapy
Systematic review

ABSTRACT

Purpose: To give recommendations on patient selection criteria for the use of accelerated partial-breast irradiation (APBI) based on available clinical evidence complemented by expert opinion.
Methods and materials: Overall, 340 articles were identified by a systematic search of the PubMed database using the keywords "partial-breast irradiation" and "APBI". This search was complemented by searches of reference lists of articles and handsearching of relevant conference abstracts and book chapters. Of these, 3 randomized and 19 prospective non-randomized studies with a minimum median follow-up time of 4 years were identified. The authors reviewed the published clinical evidence on APBI, complemented by relevant clinical and pathological studies of standard breast-conserving therapy and, through a series of personal communications, formulated the recommendations presented in this article.
Results: The GEC-ESTRO Breast Cancer Working Group recommends three categories guiding patient selection for APBI: (1) a low-risk group for whom APBI outside the context of a clinical trial is an acceptable treatment option; including patients ageing at least 50 years with unicentric, unifocal, pT1–2 ($\leqslant$30 mm) pN0, non-lobular invasive breast cancer without the presence of an extensive intraductal component (EIC) and lympho-vascular invasion (LVI) and with negative surgical margins of at least 2 mm, (2) a high-risk group, for whom APBI is considered contraindicated; including patients ageing $\leqslant$40 years; having positive margins, and/or multicentric or large (>30 mm) tumours, and/or EIC positive or LVI positive tumours, and/or 4 or more positive lymph nodes or unknown axillary status (pNx), and (3) an intermediate-risk group, for whom APBI is considered acceptable only in the context of prospective clinical trials.
Conclusions: These recommendations will provide a clinical guidance regarding the use of APBI outside the context of a clinical trial before large-scale randomized clinical trial outcome data become available. Furthermore they should promote further clinical research focusing on controversial issues in the treatment of early-stage breast carcinoma.
 Radiotherapy and Oncology 94 (2010) 264–273

Over the last three decades, breast-conserving surgery (BCS) followed by whole-breast irradiation (WBI) consisting of 5 weeks of daily external beam radiotherapy (RT) with or without additional irradiation to the tumour bed became the standard of care for the treatment of early-stage breast carcinoma [1–4]. However, the necessity of giving WBI for all patients after BCS has been questioned, and several centers have evaluated the feasibility and efficacy of accelerated partial-breast irradiation (APBI) [5–46]. The results of these clinical trials showed that APBI with proper patient selection and quality assurance (QA) yields similar results to those achieved with standard WBI [5,7,9,14,15,17,19,25,28,29,31–36,38,41,44–46]. Parallel with the growing evidence obtained from

* Corresponding author. Address: Department of Radiotherapy, National Institute of Oncology, Ráth György u. 7-9, Budapest H-1122, Hungary.
E-mail address: polgar@oncol.hu (C. Polgár).

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doi:10.1016/j.radonc.2010.01.014

phase I–II studies supporting the use of APBI for selected early-stage breast cancer patients, at least seven phase III trials comparing different techniques of APBI to conventional WBI have been initiated in the last decade in Europe, Canada and the USA [36]. The 5-year results of these randomized trials are highly awaited, but will be available only in the next 5–10 years for the radiation oncology community. Although both American and European experts encouraged the use of APBI in the context of prospective phase III trials, during the past few years the concept of APBI has been widely accepted by patients and treating physicians and more than 30,000 patients have been treated outside clinical trials worldwide [47]. Therefore, the Breast Cancer Working Group of the Groupe Européen de Curiethérapie-European Society for Therapeutic Radiology and Oncology (GEC-ESTRO) deemed it necessary to give recommendations on patient selection criteria for the use of APBI outside the context of prospective clinical trials. Recommendations were based on available clinical evidence obtained from prospective APBI studies with a minimum median follow-up time of 4 years and clinical and pathological studies of conventional breast-conserving therapy complemented by expert opinion of the authors.

It is beyond the scope of this paper to give recommendations on target definition, delineation or other technical issues of APBI delivery. Although recommendations given here are probably valid for emerging alternative techniques of APBI (e.g. 3-D external beam RT, intraoperative RT, and intracavitary brachytherapy). However it should be emphasized that the majority of available long-term clinical evidence supporting the use of APBI have been obtained from clinical trials using multicatheter interstitial brachytherapy (BT). Therefore, the validity of the statements of this paper may be limited to the multicatheter BT technique.

Material and methods

A systematic literature search was done on the PubMed database using the keywords "partial-breast irradiation" and "APBI". This search was complemented by searches of reference lists of articles and handsearching of relevant conference abstracts and book chapters. The last search was done on July 31st, 2009. Using this strategy, 340 articles were identified of which 191 were original articles (excluding reviews ($n = 110$), editorials/letters ($n = 34$), and case reports ($n = 5$). Among the 191 original articles, 75 were isolated (excluding dosimetric/technical articles ($n = 116$)). Of these, 3 randomized and 19 prospective non-randomized studies with a minimum median follow-up time of 4 years were identified. The authors reviewed the published clinical evidence on APBI, complemented by relevant clinical and pathological studies of standard breast-conserving therapy and, through a series of personal communications, formulated the recommendations presented in this article.

Rationale for APBI

In the last two decades APBI using interstitial or intracavitary implants, 3-D conformal external beam RT or intraoperative RT has been intensively evaluated in prospective clinical trials as a possible alternative to conventional WBI [9,33,36,45,48–50]. The rationale for APBI is as uniformly reported that the majority of local recurrences (LRs) occur in proximity to the tumour bed [33,45,51,52]; less than 20% of LRs appear "elsewhere" in the breast, and the absolute number of such failures is very low (e.g. far less than 1% per year and similar to the rate of new contralateral tumours) [3,4]. In addition, some elsewhere failures are diagnosed as likely to be new primary breast cancer that arose after initial therapy and hence would not have been prevented by WBI [44].

APBI is regarded as an attractive treatment approach that shortens the 5–7-week course of conventional postoperative RT to 4–5 days [4,33,36,45]. The acceleration of RT is considered to eliminate some of the disadvantages of the long treatment period, especially for elderly patients, working women, and those who live at a significant distance from the RT facility [33,36,45].

Clinical results of APBI using suboptimal patient selection

Several centers pioneered the use of different APBI regimens for unselected patients in 1980s and early 1990s [10–13,16,20,26,30,37]. However, results in all these early studies were poor, with high LR rates exceeding 1% per year (Table 1). The high rates

Table 1
Results of APBI studies using suboptimal patient selection criteria with adequate ($\geqslant$4 years) follow-up.

Institution	Technique	Median FUP (years)	LR% (n)	Annual LR% (n)	Comments on patient selection
Uzsoki hospital [37]	MDR	12	24 (17 of 70)	2	Max. tumour size: 5 cm; 100% unknown margins; 30% unknown pathological axillary status (pNx); 4% node positive; 10% lobular ca.; multifocal tumours, LVI and EIC allowed; no patient age limitation
Christie hospital[a] [20]	EBI	8	20 (69 of 353)	2.5	Max. tumour size: 4 cm; 100% unknown margins; no surgical axillary staging; lobular ca., LVI and EIC allowed; no patient age limitation
Cookridge hospital[a] [11]	EBI	8	12 (10 of 84)	1.5	Max. tumour size: 4.5 cm; 41% node positive; lobular ca., LVI and EIC allowed; no patient age limitation
London Reg. Ca. C. [30]	HDR	7.6	15 (6 of 39)	2	Max. tumour size: 4.5 cm; 31% close margins; 15% node positive; 5% pNx; 8% EIC pos.; no patient age limitation
Tufts university [16]	HDR	7	9.1 (3 of 33)	1.30	45% Close margins; 9% node positive; 55% EIC pos.; no patient age limitation
Guy's hospital I [12]	LDR	6	37 (10 of 27)	6.2	Max. tumour size >4 cm; 56% positive margins; 44% node positive, 41% EIC positive; lobular ca. and LVI allowed; patient age >40 years
Guy's hospital II [13]	MDR	6.3	18 (9 of 49)	2.9	Max. tumour size: 4 cm; 43% positive margins; 45% node positive; 14% lobular ca., LVI and EIC allowed, no patient age limitation
Osaka Med. center [26]	HDR	4.3	5.0 (1 of 20)	1.15	15% Positive margins; 35% EIC pos.; 5% lobular ca.; 10% DCIS; no patient age limitation (25% with age $\leqslant$45 years)
Florence hospital [10]	LDR	4.2	6 (7 of 115)	1.4	Max. tumour size: 5 cm; 8% positive and 7% unknown margins; 38% node positive; 20% lobular ca.; LVI and EIC allowed, no patient age limitation
All patients		4.2–12	17 (132 of 790)	1.15–6.2	

APBI = accelerated partial-breast irradiation; FUP = follow-up period; LR = local recurrence; EIC = extensive intraductal carcinoma; LVI = lympho-vascular invasion; EBI = external beam irradiation; MDR = medium-dose rate; LDR = low-dose-rate; HDR = high-dose-rate.
[a] Randomized trial.

of local failure seen in these early APBI studies reflect inadequate patient selection criteria and/or suboptimal treatment technique and lack of appropriate QA procedures [53,54]. Hence, a large amount of the patients treated in these studies would not be considered eligible for breast-conserving therapy today. Therefore, the results of these early clinical trials cannot be used to disparage the concept of APBI, if performed with appropriate technique and stringent patient selection.

Clinical results of APBI using strict patient selection criteria for low-risk early breast cancer

Based on the controversial results of earlier studies, several groups designed APBI trial protocols incorporating more strict patient selection criteria including only low-risk early breast cancer and systematic QA procedures [33,36,45]. As a result, the outcomes of these studies have been improved considerably (Table 2) [5,7,9,14,15,17,19,25,28,29,31–36,38,41,44]. Long-term results of these trials proved similar efficacy of APBI in preventing LR to those achieved in other breast-conserving series using conventional WBI. It is to be noted that consequently low rate of LR has been reported (e.g. far less than 1% per year) in all contemporary series cited in Table 2. Furthermore, good to excellent cosmetic results in all studies but one have been reported in the range of 75–99% using multicatheter interstitial BT [5,7,9,14,17,19,25,28,29,31–36,38,41,44].

Based on the encouraging results of these phase I–II APBI trials, seven prospective phase III clinical trials have been activated to compare the efficacy of APBI to conventional WBI [36]. Among these, the 5-year results of the Hungarian single-institution randomized APBI study were reported in 2007 [34]. In this trial, 258 patients had been randomized to receive either 50 Gy WBI ($n = 130$) or partial-breast irradiation (PBI, $n = 128$). The latter consisted of either 36.4 Gy (given over 4 days using seven fractions of 5.2 Gy each) with high-dose-rate (HDR) multicatheter BT ($n = 88$) or limited-field electron beam (EB) irradiation ($n = 40$) giving a dose of 50 Gy in 25 fractions over 5 weeks. In the most recent

Table 2
Results of APBI studies using stringent patient selection criteria with adequate ($\geqslant$4 years) follow-up.

Institution/study	Technique	Median FUP (years)	LR% (n)	Annual LR%	Comments on patient selection
HNIO, Budapest I [32,33,35,36]	HDR	11.1	8.9 (4 of 45)	0.80	Max. tumour size: 2 cm; clear margins; unifocal tumour; grade I–II; pN0 or pN1mi; no patient age limitation. *Excluded:* lobular ca., DCIS and EIC
WBH, Michigan [5,44]	LDR/HDR	9.7	5.0 (10 of 199)	0.52	Max. tumour size: 3 cm; margins $\geqslant$ 2 mm; pN0; patient age >40 years. *Excluded:* lobular ca., DCIS, and EIC
Örebro Med. Centre [15]	PDR	7.2	5.9 (3 of 51)	0.83	Max. tumour size: 4.2 cm; clear margins; unifocal tumour; 12% node pos. (1–3 nodes); 8% lobular ca.; patient age $\geqslant$ 40 years. *Excluded:* DCIS and EIC
RTOG 95–17 [7]	LDR/HDR	7	6.1 (6 of 99)	0.91	Max. tumour size: 3 cm; clear margins; unicentric tumour; 20% node positive (1–3 pos. nodes without ECE); no patient age limitation. *Excluded:* lobular ca., DCIS, and EIC
HNIO, Budapest II[a] [33–36]	HDR/EBI	6.8	4.7 (6 of 128)	0.69	Max. tumour size: 2 cm; margins $\geqslant$ 2 mm; unifocal tumour; grade I–II; pN0 or pN1mi; patient age >40 years. *Excluded:* lobular ca., DCIS, and EIC
Ochsner clinic [17]	LDR/HDR	6.25	2 (1 of 51)	0.32	Max. tumour size: 4 cm; clear margins; unicentric tumour; 18% node positive (1–3 nodes); 10% DCIS; 14% EIC; no patient age limitation
Ninewells hospital [38]	LDR	5.6	0 (0 of 11)	0	Max. tumour size: 3.5 cm; unifocal tumour, pN0 or pN1a (only 1 pt. node pos.); patient age >40 years. *Excluded:* lobular ca., DCIS, and EIC
Germany–Austria [28,41]	PDR/HDR	5.25	2.9 (8 of 274)	0.55	Max. tumour size: 3 cm; margins $\geqslant$2 mm; unifocal tumour; grade I–II; pN0 or pN1mi; ER or PgR pos.; 16% lobular ca.; patient age >35 years. *Excluded:* DCIS, EIC and LVI
FDA Trial, USA [9]	MammoSite	5.2	0 (0 of 43)	0	Max. tumour size: 2 cm; clear margins; unifocal tumour; pN0; patient age $\geqslant$45 years. *Excluded:* lobular ca., DCIS, and EIC
Kiel-HNIO [25,36]	MammoSite	5	0 (0 of 11)	0	Max. tumour size: 2 cm; margins $\geqslant$5 mm; unifocal tumour; grade I–II; pN0; ER or PgR pos.; patient age $\geqslant$60 years. *Excluded:* lobular ca., DCIS, EIC and LVI
University Navarra [14]	HDR	4.4	3.8 (1 of 26)	0.86	Max. tumour size: 3 cm; margins $\geqslant$2 mm; unicentric tumour; pN0; no patient age limitation *Excluded:* lobular ca., DCIS, and EIC
Wisconsin university [29]	HDR/ MammoSite	4	2.9 (8 of 273)	0.72	Max. tumour size: 3 cm; margins $\geqslant$ 2 mm; unicentric tumour; 7% node positive (1–3 nodes without ECE); 13% DCIS; no patient age limitation. *Excluded:* lobular ca. and EIC.
Kansas university [19]	LDR	4	0 (0 of 25)	0	Max. tumour size: 2 cm; clear margins; grade I–II, pN0; 12% (classical) lobular ca.; patient age $\geqslant$60 years. *Excluded:* non-classical lobular ca., DCIS and EIC
All patients		4–11.1	3.8 (47 of 1236)	0–0.91	

APBI = accelerated partial-breast irradiation; FUP = follow-up period; LR = local recurrence; EIC = extensive intraductal carcinoma; LVI = lympho-vascular invasion; DCIS = ductal carcinoma in situ; ECE = extracapsular extension; ER = estrogen receptor; PgR = progesterone receptor; LDR = low-dose-rate; HDR = high-dose-rate; EBI = external beam irradiation; FDA = food and drug administration; HNIO = Hungarian National Institute of Oncology; RTOG = Radiation Therapy Oncology Group; WBH = William Beaumont hospital.

[a] Randomized trial.

Table 3
Seven-year actuarial results of the Budapest phase III APBI trial.

Treatment arm	LR% (*n*)	RR% (*n*)	CSS%	DFS%	DMFS%
PBI	5.1 (6 of 128)	1.6 (2 of 128)	96.2	86.3	91.0
WBI	3.3 (4 of 130)	1.7 (2 of 130)	93.9	89.0	92.3
p-Value	0.53	0.99	0.45	0.65	0.94

APBI = accelerated partial-breast irradiation; PBI = partial-breast irradiation; WBI = whole-breast irradiation; LR = local recurrence; RR = regional recurrence; CSS = cancer-specific survival; DFS = disease-free survival; DMFS = distant metastasis-free survival.

analysis, at a median follow-up time of 6.8 years, there has been no significant difference in local and regional tumour control, disease-free, cancer-specific or distant metastasis-free survival between the two treatment arms (Table 3) [35,36]. The rate of excellent to good cosmetic result was 77% in the PBI group (81% after HDR BT; 68% after EB) and 65% in the control group ($p_{WBI/PBI} = 0.024$) [34–36]. It has been also proven that the incidence of fat necrosis was similar after conventional WBI and accelerated partial-breast HDR BT [55].

Patient-, tumour- and treatment-related factors affecting decision making in patient selection for APBI

Patient age

Young age has been documented to be a dominant adverse prognostic factor for in-breast LR [1,52,56–58]. Most series reported an increased breast failure rate using a variety of age cut-offs. The European Organization for Research and Treatment of Cancer (EORTC) boost trial demonstrated that young age was the most important prognostic factor for LR [1]. The largest clinical benefit from boost was seen in patients younger than 41 years: at 10 years their LR rate was reduced from 23.9% to 13.5%. In the age groups 41–50, 51–60, and above 60 years boost reduced 10-year LR rate from 12.5% to 8.7%, from 7.8% to 4.9%, and from 7.3% to 3.8%, respectively. In the Budapest boost trial, age less than 40 years was also found to be an independent prognostic factor for LR [58–60]. The actuarial 5-year LR rate after 50 Gy WBI (with or without a boost dose of 16 Gy) was 30.8% for younger women and 7.3% for patients above 40 years ($p < 0.0001$; relative risk; RR: 5.25). These results suggest that there is a distinct biological difference in breast carcinoma presenting in young women that predisposes them to LR. Taking into account the higher absolute benefit of boost in patients younger than the age of 50 years, it seems to be justified to give a tumour bed dose exceeding 60 Gy for these women. As in all APBI series a hypofractionated dose schedule biologically equivalent to 50 Gy conventionally fractionated WBI (without boost) was used, it seems to be logical to offer APBI outside the context of a clinical trial to patients older than 50 years of age. This is also supported by the fact that a majority of patients treated in prospective APBI trials were older than 50 years [5,7,29,31–36,41].

According to the collective experience from modern APBI series, patients above 50 years can be treated successfully with a 50 Gy equivalent dose yielding an annual LR rate below 1% (see Table 4). However, conflicting results have been reported for patients ageing 41–50 years. For this intermediate age group an encouraging crude LR rate of 2.6% at 7 years and 4.3% at 10 years was observed in the Hungarian and William Beaumont series, respectively. In contrast, a relatively high LR rate was reported in the German–Austrian (8.7% at 5 years), Wisconsin University (6.1% at 5 years), Radiation Therapy Oncology Group (RTOG) 95–17 (19% at 7 years), and Örebro University (12.5% at 7 years) trials. Therefore, further prospective studies are needed to justify the use of APBI for women between the age of 41 and 50 years. In the Hungarian phase I–II APBI trial patient age of 40 years or less was found to be the most important negative prognostic factor for LR [35,36]. The 5-year actuarial rate of LR for patients below the age of 41 was 22.2% in contrast to older women with a corresponding LR rate of 3% ($p = 0.016$; RR: 6.69). Furthermore, most APBI series not using an age limitation failed (see Table 1), and very young patients (e.g. younger than 40 years) were excluded from successful studies (see Table 2). Based on these considerations, patients below the age of 40 years should not be candidates for APBI.

Invasive lobular carcinoma (ILC) and lobular carcinoma in situ (LCIS)

ILC was thought to be a relative contraindication for breast conservation for decades, due to its multifocality and diffuse pattern of spreading [61]. However, others reported that multicentric lesions were not significantly more frequent in ILC and long-term results from the nineties proved that adequate surgery and RT for ILC maintained similar local tumour control (LTC) as for ductal cancers (Table 5) [52,62–71]. The site of in-breast failure relative to the location of the original tumour was also not significantly different between lobular and non-lobular carcinomas (Table 5) [63,66,68,70,71].

In the Christie Hospital study, the LR rate for patients treated with sole tumour bed RT for ILCs was as high as 43% [20]. One could however argue that many of the patients treated in this trial were not acceptable candidates for breast-conserving therapy in general (e.g. unknown surgical margins, and lack of axillary staging). On the other hand, in the current APBI series using careful pathologic assessment of margin status tumour bed BT alone maintained adequate LTC for patients with ILC, too [15,19,28,41].

Table 4
Local recurrence rate as a function of patient age in prospective APBI studies.

Age (years)	HNIO phase II–III [31–36][a] Crude LR% (*n*)	German–Austrian phase II [41] Crude LR% (*n*)	WBH phase II [5] Crude LR% (*n*)	Wisconsin university Phase II [29][b] Crude LR% (*n*)	RTOG 95–17 Phase II [7] Crude LR% (*n*)	Örebro university Phase II [15][d] Crude LR% (*n*)	All studies crude LR% (*n*)
⩽40	33.3% (2 of 6)	0% (0 of 3)	0% (0 of 1)	0% (0 of 8)	NR[c]	0% (0 of 1)	10.5% (2 of 19)
>40–50	2.6% (1 of 39)	8.7% (4 of 46)	4.3% (1 of 23)	6.1% (4 of 66)	19% (4 of 21)[c]	12.5 (2 of 16)	7.6% (16 of 211)
>50–60	6.9% (4 of 58)	1.2% (1 of 82)	8.7% (4 of 46)	2.2% (2 of 93)	4.2% (1 of 24)	0% (0 of 19)	3.7% (12 of 322)
>60	4.3% (3 of 70)	2.1% (3 of 143)	3.9% (5 of 129)	4.2% (5 of 120)	1.8% (1 of 54)	6.7 (1 of 15)	3.4% (18 of 531)
All age	5.8% (10 of 173)	2.9% (8 of 274)	5.0% (10 of 199)	3.8% (11 of 286)	6.1% (6 of 99)	5.9% (3 of 51)	4.4% (48 of 1083)
FUP	7.3 years	5.25 years	9.7 years	5 years	7 years	7.2 years	NA

APBI = accelerated partial-breast irradiation; HNIO = Hungarian National Institute of Oncology; WBH = William Beaumont hospital; RTOG = Radiation Therapy Oncology Group; LR = local recurrence; FUP = median follow-up period; NR = not reported; NA = not applicable.

[a] Updated results by Polgar C.
[b] Updated results by Patel R.
[c] Results for patients ⩽40 years and >40–50 years were reported together.
[d] Updated results by Johansson B.

Table 5
Incidence and site of local recurrence following breast-conserving therapy for lobular and non-lobular carcinomas.

Author	FUP (years)	ILC		IDC	
		LR%	TR/MM%	LR%	TR/MM%
Sastre-Garau [67]	10	20	NR	22	NR
Peiro [66]	10	15	86	13	78
Warneke [70]	5	3	NR	–	–
Weiss [71]	5	9	100	7	71
Schnitt [68]	6.25	14	100	12	80
Fodor [63]	15	13	93	–	–
Silverstein [69]	6.6	5	NR	5	NR
All studies	5–15	3–20	86–100	5–22	71–80

FUP = follow-up period; ILC = invasive lobular carcinoma; IDC = invasive ductal carcinoma; LR = local recurrence; TR/MM = true recurrence/marginal miss; NR = not reported.

Among the 274 patients enrolled into the German–Austrian APBI study 45 patients (16%) had ILC, and there was no significant difference in the 5-year LR rate of patients with ILC compared to other histologies [28,41]. Based on these considerations, one can conclude that the presence of ILC should not influence decisions regarding local therapy, and patients with ILC can be successfully treated with BCS and APBI. However, to date only few women having ILC have been treated with APBI in prospective studies. Therefore, at this time there is only a limited evidence for the treatment of ILC outside the context of clinical trials.

On the other hand, small cell LCIS associated with an invasive tumour should not be considered as a contraindication neither for breast-conserving therapy nor for APBI [68].

Ductal carcinoma in situ (DCIS)

Treatment of women with DCIS by APBI is also controversial, since according to pathologic and clinical studies a significant proportion of these tumours are widely spread in the breast and multifocality is a significant predictor of LR [72,73]. On the other hand, Faverly et al. [74], using computer-assisted three-dimensional reconstruction of the mammary ductal tree, found that DCIS was unicentric in the majority (>95%) of the cases, extending by continuous or discontinuous growth along the ducts in a segmental pattern. Although, discontinuous growth was present in 50%, the gaps between these separated foci were less than 10 mm in 92% of the cases. These data suggest that, if adequate margins are taken by the surgeons and radiation oncologists, good local control might be expected with APBI [75]. Therefore, small (<3 cm), unifocal DCIS excised with adequate margins is considered acceptable to be treated with APBI by some radiation oncologists [17,29]. Recently, the American Society of Breast Surgeons reported that in their MammoSite BT trial the 3-year actuarial rate of LR was only 2.4% for DCIS and 2.1% for invasive breast carcinoma [76]. However, 11 of the 13 successful APBI trials with extended ($\geqslant$4 years) follow-up excluded patients with DCIS (see Table 2). Thus, further prospective studies are needed to justify the use of APBI for selected low-risk DCIS patients.

Histologic grade (HG)

The value of HG as a prognostic factor for LR is also controversial. Clarke et al. [51] found that high grade was a strong predictor for LR. Van Limbergen et al. [52] noted 5-year local control rates of 95% for grade I, 90% for grade II, and 84% for grade III tumours, but the differences were not statistically significant ($p = 0.12$) and was correlated to young age in a multivariate analysis. In the Hungarian boost vs no boost trial HG had no significant impact on LTC [58–60]. However, the mean time to LR was shorter for grade III tumours (20 months) than for grade I–II carcinomas (38 months). These data suggest that poorly differentiated malignant cells remaining in the breast following the excision of high-grade tumours tend to regrow more rapidly than highly differentiated cells in low-grade tumours. However, there is no clear evidence proving that high-grade tumours would spread more widely in the ductal tree compared to low-grade carcinomas. Based on these considerations, in most APBI studies tumours with any HG were enrolled and treated with consecutive adequate LTC (see Table 2) [5,7,9,14,15,17,28,29,38,41,44].

Tumour size (pT)

Although in the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-06 trial patients with T2 tumours were more likely to develop LR following BCS without RT, in most series tumour size did not affect the LTC significantly following BCS with RT [52,59,60,62,77,78]. This corresponds to the pathology data from Holland et al. [72], showing that the microscopic spread beyond the primary tumour is similar in T1 and T2 tumours.

In early APBI studies tumours up to a diameter of 4–5 cm were treated by tumour bed RT alone (see Table 1) [9–13,16,20,26,30,37]. However, in the majority of contemporary APBI series maximum tumour size was limited to 3 cm (see Table 2) [5,7,9,14,19,25,28,29,31–36,38,41,44]. Some investigators experienced that at large-volume (>160 cm^3) interstitial BT implants the larger implant volume (V100) and high-dose regions (V150 and V200) were correlated with a higher incidence of late soft tissue toxicity (e.g. fat necrosis) [79–81]. Based on these clinical observations large tumours (>3 cm) might not be candidates for partial breast BT alone, because of the high risk of fat necrosis caused by large volume implants.

Obviously, patients with T3 or T4 tumours are not candidates for primary breast-conserving therapy. Therefore, these women should not be treated with APBI.

Surgical margin status

Positive margin status is generally accepted as a major risk factor for LR after BCS and RT [58,82–86]. Furthermore, the number of positive margins as well as the width of clear surgical margins significantly influences LTC [58,83,84]. In the study of Schnitt et al. [84] the 5-year breast failure rate was 0%, 4%, 6% and 21% with clear, close, focally positive, and diffusely positive surgical margins, respectively. In the Hungarian boost trial the respective rates with clear, close ($\leqslant$2 mm), and positive margins were 8%, 30%, and 35%, and in case of positive or close margins a boost dose of 16 Gy following 50 Gy WBI decreased the incidence of LR from 47% to 8% [58–60]. These clinical results are consistent with the pathological findings showing that the amount of microscopic tumour cells decreases with the distance from the primary tumour [72].

In the majority of early APBI studies patients with positive or unknown surgical margins were eligible, which resulted in an unacceptably high LR rate (see Table 1) [10–13,20,26,37]. Later at least 2 mm tumour-free margins were deemed acceptable in some APBI trials [5,14,25,28,29,34,41,44], but others were also successfully treated patients with close margins by sole tumour bed BT [7,9,15,17,19,32] (see Table 2). However, there are only limited data supporting the use of APBI for patients with close (but clear) surgical margins.

Multifocality, multicentricity

It is evident that patients with multicentric tumours (defined as the presence of separate tumour foci more than 2 cm from the

index cancer) should not be treated with APBI because the extent of disease cannot be covered by PBI.

On the other hand, unicentric but multifocal tumours (defined as separate tumour foci within 2 cm of the index lesion) may be treated successfully with APBI [7,14,17,29]. However, there is no published experience regarding the outcome in this subgroup of patients. Therefore, only unicentric-unifocal tumours should be considered eligible for APBI outside the context of clinical trials.

Extensive intraductal component (EIC)

EIC is usually reported when 25% or more of an invasive ductal cancer consist of intraductal carcinoma and ductal carcinoma in situ is also present in the adjacent breast tissue. Holland et al. [72,87] reported that patients with EIC were more likely to have residual tumour beyond 2 cm distance from the reference tumour than without EIC (33% vs 2%, respectively). The amount of residual tumour was also correlated with the presence of EIC. These findings explain why patients with EIC positive tumours were more likely to fail locally following BCS and RT (Table 6) [58,62,77,88–90].

According to the 4-year clinical update from the American Society of Breast Surgeons MammoSite APBI trial, out of multiple variables examined for potential association with ipsilateral breast failure, only the presence of an EIC was associated with the development of a LR [76]. As a consequence, EIC is also regarded as a contraindication for APBI by most authors.

Hormone receptor status

Despite the large body of literature supporting the routine use of hormone receptor status in clinical decision making for systemic management, the role of hormone receptors as prognostic factors for LR is relatively weak and unexplored [91]. The results of some studies are summarized in Table 7 [92–96]. Several other studies have also failed to show significant correlation between the incidence of LR and hormone receptor status [97,98].

To date, only the German–Austrian phase II and the German–Hungarian MammoSite APBI studies did not enroll patients with ER and PR negative tumours [25,28,41]. In all other successful European and American studies negative hormone receptor status was not a contraindication for APBI [5,7,9,14,15,17,19,29,31–36,38,44]. Considering these data, to date there is no existing evidence suggesting that patients with hormone receptor negative tumours would be ineligible for APBI.

Lympho-vascular invasion (LVI)

Peritumoral LVI has been reported by numerous authors as a risk factor for LR [60,99,100]. In the Budapest boost trial LVI caused a twofold higher risk for intrabreast relapse (5-year LTC: 12.5% vs 6.2%; $p = 0.03$) [60]. Extrapolating from the assumption that in the presence of LVI malignant cells can spread widely in the breast via lympho-vascular spaces, it seems appropriate to be conservative, and treat only patients without LVI with APBI.

Table 6
Incidence of local recurrence according to extensive intraductal component following breast-conserving therapy.

Author	FUP (years)	LR%		Tumour bed dose (Gy)
		EIC+	EIC−	
Wazer [88]	7	12	3	50–70.4
Fowble [89]	10	22	4	60–70
Eberlein [77]	10	27	7	>60
Krishnan [90]	10	9	5	60–70
Fodor [62]	10	27	7	50
Polgár [58]	5	16	10	50–66
All studies	5–10	9–27	3–10	50–70.4

FUP = follow-up period; LR = local recurrence; EIC = extensive intraductal component.

Table 7
Incidence of local recurrence according to hormone receptor status.

Author	Patient no.	Surgery	RT	Finding
Sundquist [92]	629	MAST	±	Trend towards higher LR rate with ER neg. status; LR: ER neg.: 12.7% vs ER pos.: 6.3% ($p = 0.12$)
Zellars [93]	1530	MAST	±	Higher LR rate with ER neg. status in no RT group; LR: ER neg.: 16.4% vs ER pos.: 12.0% ($p = 0.04$); but no correlation in irradiated group!
Fisher [94]	150	MAST/ BCS	–	Higher LR rate in combined ER and PR neg. patients
Silvestrini [95]	1800	MAST/ BCS	±	No correlation between ER status and LR rate
Elkhuizen [96]	195	BCS	+	Higher frequency of PR neg. tumours in patients with LR (75% vs 60%; $p = 0.03$)
Polgár[a]	342	BCS	+	No significant difference in LR rate according to ER and PR status LR: ER neg.: 13.3% vs ER pos.: 9.9% ($p = 0.50$); LR: PR neg.: 14.3% vs PR pos.: 8.9% ($p = 0.19$)

RT = radiotherapy; MAST = mastectomy; BCS = breast-conserving surgery; ER = estrogen receptor; PR = progesterone receptor; LR = local recurrence.
[a] Unpublished results from the Budapest boost trial by Polgar C.

Surgical nodal staging – pathologic axillary status (pN)

In the majority of early APBI trials surgical nodal staging was incomplete (or fully avoided), and these studies reported a high incidence of LR (see Table 1) [11,20,30,37]. Therefore, candidates for APBI should undergo either sentinel lymph node biopsy or axillary dissection.

The treatment of node-positive patients with PBI is also controversial. Women with less than 4 involved axillary lymph nodes with or without extracapsular extension were also considered for partial breast BT in some APBI series [7,15,17,29,38]. Other groups (including successful European APBI studies) selected only patients with negative or not more than microscopically involved lymph nodes [5,9,14,19,25,28,33–36,41,44]. Furthermore, patients with positive lymph nodes have not only a higher risk of LR but also a higher risk of developing distant metastases and dying of breast cancer [101]. According to the meta-analysis of the Early Breast Cancer Trialists' Collaborative Group (EBCTCG), RT after BCS results in a 15-year survival benefit of 7.1% for patients with positive lymph nodes (including all patients with pN1–3 axillary status) [101]. Although no subgroup analysis was performed for patients with 1–3 positive nodes (pN1a cases), one cannot exclude a possible survival benefit of WBI for such patients with limited axillary disease. Therefore, it seems to be safe not to treat patients with involved axillary lymph nodes with APBI outside the context of prospective clinical trials.

Neoadjuvant chemotherapy

Due to the lack of studies evaluating the feasibility of APBI following neoadjuvant chemotherapy and BCS, such patients should not receive APBI.

GEC-ESTRO recommendations on patient selection for APBI

Based on the published clinical results of APBI and the experience obtained from clinical and pathological studies of breast-conserving therapy, the GEC-ESTRO Breast Cancer Working Group recommends three categories guiding patient selection for APBI:

Low-risk group

Low-risk patients meeting all criteria described in Table 8/A should be good candidates for APBI outside the context of prospective clinical trials. For these women APBI or WBI can be offered as alternative treatment options following BCS in the daily routine practice. Patients choosing treatment with APBI should be fully informed that WBI is an established treatment that has documented long-term efficacy with low-risk of early and late side-effects. Patients should be also familiar with the possible risks and benefits of APBI taking into account the lack of long-term results (beyond 10 years) with APBI.

Patient age >50 years was selected as the cutoff for the low-risk group, because in all successful APBI studies (see Table 4) patients above 50 years experienced consequently low rate of LR (e.g. an annual LR rate of 0–0.95%).

Based on pathological considerations patients having tumours with any HG were considered eligible for APBI and were included in the low-risk group.

Tumour size of ⩽3 cm was selected as the cutoff for the low- and intermediate-risk groups because in the majority of contemporary APBI series maximum tumour size was limited to 3 cm.

Based on pathological considerations, only patients with unicentric-unifocal tumours and clear surgical margins of at least 2 mm were included in the low-risk group.

Patients with any hormone receptor status were placed in the low-risk group because in the majority of successful APBI studies both ER (and PR) positive and negative tumours were enrolled and treated with consecutive adequate LTC.

Only patients having pathologically negative axillary lymph nodes documented by either sentinel lymph node biopsy or axillary dissection were included in the low-risk group because high LR rates were reported in early APBI trials with incomplete surgical nodal staging (see Table 1).

Intermediate-risk group

The intermediate-risk group of patients (Table 8/B) not meeting all criteria of the first category, but thought to be potentially good candidates for APBI should be treated with APBI only in the context of prospective clinical trials.

Women aged 41–50 years were included in the intermediate-risk group because, although a majority of APBI trials have attempted to include such patients, relatively few patients ($n = 211$) have been actually enrolled in such trials (see Table 4), and conflicting results have been reported for this age group (e.g. an annual LR rate of 0.36–1.74%). Thus, it was felt that further prospective studies are needed to justify the use of APBI for women between the age of 41 and 50 years.

Although in the German–Austrian APBI study there was no significant difference in the 5-year LR rate of patients with ILC compared to other histologies [29,44], however to date only few women having ILC have been treated with APBI in prospective studies. Therefore, at this time there is only a limited evidence for the treatment of ILC outside the context of clinical trials. Thus, patients having ILC were included in the intermediate-risk group.

Although preliminary (3-year) experience of the American Society of Breast Surgeons with APBI for the treatment of patients having pure DCIS is promising [76], patients with DCIS were also placed in the intermediate-risk group because of the lack of available long-term evidence supporting the routine use of APBI for such patients.

Patients with close (<2 mm) but negative margins were included in the intermediate-risk group because there were only limited experience to define whether such patients could safely be treated with APBI.

Unicentric but multifocal tumours (defined as separate tumour foci within 2 cm of the index lesion) were included in the intermediate-risk group because theoretically the extent of the microscopic residual disease could be covered by partial-breast irradiation. However, there is no published experience regarding the outcome in this subgroup of patients.

Although women with 1–3 positive axillary lymph nodes were also considered for partial-breast irradiation in some APBI series, such patients were placed in the intermediate-risk group because one could not exclude a possible survival benefit of WBI for such

Table 8
GEC-ESTRO recommendations on patient selection for accelerated partial-breast irradiation.

Characteristic	A/low-risk group – good candidates for APBI	B/intermediate-risk group – possible candidates for APBI	C/high-risk group – contraindication for APBI
Patient age	>50 years	>40–50 years	⩽40 years
Histology	IDC, mucinous, tubular, medullary, and colloid cc.	IDC, ILC, mucinous, tubular, medullary, and colloid cc	–
ILC	Not allowed	Allowed	–
Associated LCIS	Allowed	Allowed	–
DCIS	Not allowed	Allowed	–
HG	Any	Any	–
Tumour size	pT1–2 (⩽30 mm)	pT1–2 (⩽30 mm)	pT2 (>30 mm), pT3, pT4
Surgical margins	Negative (⩾2 mm)	Negative, but close (<2 mm)	Positive
Multicentricity	Unicentric	Unicentric	Multicentric
Multifocality	Unifocal	Multifocal (limited within 2 cm of the index lesion)	Multifocal (>2 cm from the index lesion)
EIC	Not allowed	Not allowed	Present
LVI	Not allowed	Not allowed	Present
ER, PR status	Any	Any	–
Nodal status	pN0 (by SLNB or ALND[a])	pN1mi, pN1a (by ALND[a])	pNx; ⩾pN2a (4 or more positive nodes)
Neoadjuvant chemotherapy	Not allowed	Not allowed	If used

APBI = accelerated partial-breast irradiation; IDC = invasive ductal carcinoma; ILC = invasive lobular carcinoma; LCIS = lobular carcinoma in situ; DCIS = ductal carcinoma in situ; HG = histologic grade; EIC = extensive intraductal component; LVI = lympho-vascular invasion; ER = estrogen receptor; PR = progesterone receptor; SLNB = sentinel lymph node biopsy.

[a] ALND = axillary lymph node dissection (at least 6 nodes pathologically examined).

patients with limited axillary disease. Therefore, it seems to be safe not to treat patients with involved axillary lymph nodes with APBI outside the context of prospective clinical trials.

High-risk group

The high-risk group of women (Table 8/C) should not be treated with APBI, as there is enough evidence against the use of APBI for such patients. These women should be treated with WBI with or without tumour bed boost according to available clinical evidence [1,58].

Patients ageing $\leqslant$40 years were considered ineligible for APBI because in the Hungarian phase I–II APBI trial patient age of 40 years or less was found to be the most important negative prognostic factor for LR [58–60]. Furthermore, most APBI series not using an age limitation failed (see Table 1), and very young patients (e.g. younger than 40 years) were excluded from successful studies (see Table 2).

Patients with T3 or T4 tumours are not candidates for primary breast-conserving therapy. Patients with T2 tumours larger than 3 cm have a high risk for developing fat necrosis caused by large volume implants used to cover the excision cavity with adequate margins. Therefore, these women should not be treated with APBI.

Patients with positive or unknown margins were placed in the high-risk group because in the majority of early APBI studies such patients experienced an unacceptably high LR rate (see Table 1).

Patients with multicentric tumours should be considered ineligible for APBI because the extent of microscopic residual disease cannot be encompassed by partial-breast irradiation.

Based on pathological considerations patients with EIC or LVI positive tumours were included in the high-risk group because such patients were more likely to have residual tumour beyond 2 cm distance from the index lesion (which could be covered by partial-breast irradiation).

Patients with 4 or more positive axillary lymph nodes were also considered ineligible for APBI because locoregional external beam RT was deemed mandatory for such patients.

Taking into account the lack of clinical studies evaluating the feasibility of APBI following neoadjuvant chemotherapy and BCS, such patients were also included in the high-risk group.

Conclusions

Based on the available evidence from prospective clinical trials with excellent results in selected patient groups, it seems to be justified to recommend APBI outside clinical trials if strict patient selection criteria are applied including only low-risk early breast cancer and if systematic QA procedures are followed for indication and treatment performance. These recommendations provide clinical guidance for physicians and patients to use or not to use APBI outside clinical trials and promote further clinical research focusing on controversial issues in the radiation therapy of early-stage breast carcinoma.

Remarks

These recommendations were prepared by the members of the GEC-ESTRO Breast Cancer Working Group on the basis of information available at the time of writing the manuscript. Therefore, these recommendations will require periodical update when new knowledge regarding APBI becomes available. The GEC-ESTRO Breast Cancer Working Group assumes no liability for the information, conclusions, and findings contained in its recommendations. It is also to be noted that adherence to the recommendations will not ensure successful treatment in every situation. The medical judgement regarding any specific therapy must be made by the physician and patient considering all aspects of the medical records presented by the individual patient.

Acknowledgements

The authors thank Drs. Frank A. Vicini (William Beaumont Hospital, Royal Oak, MI, USA), Douglas W. Arthur (Virginia Commonwealth University, Richmond, VA, USA), and Rakesh R. Patel (University of Wisconsin Hospital and Clinics, Madison, WI, USA) for giving their updated results for Table 4 of the article.

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