# European Society for Radiotherapy and Oncology Advisory Committee in Radiation Oncology Practice consensus recommendations on patient selection and dose and fractionation for external beam radiotherapy in early breast cancer

**European Society for Radiotherapy and Oncology (ESTRO) Advisory Committee in Radiation Oncology Practice (ACROP) consensus recommendations on patient selection and dose/fractionation for external beam radiation therapy in early breast cancer**

Icro Meattini, MD [1,2,*], Carlotta Becherini, MD [1,2], Liesbeth Boersma, MD [3], Orit Kaidar-Person, MD [3,4], Gustavo Nader Marta, MD [5,6], Angel Montero, MD [7], Birgitte Vrou Offersen, MD [8], Marianne C. Aznar, PhD [9,10], Claus Belka, MD [11], Adrian Murray Brunt, FRCR [12,13], Samantha Dicuonzo, MD [14], Pierfrancesco Franco, MD [15,16], Mechthild Krause, MD [17-21], Mairead MacKenzie, Mrs [22], Tanja Marinko, MD [23,24], Livia Marrazzo, MSc [25], Ivica Ratosa, MD [23,24]; Astrid Scholten, MD [26], Elżbieta Senkus, MD [27,28], Hilary Stobart, Mrs [22], Philip Poortmans, MD [29,30,°], and Charlotte E. Coles, FRCR [31,°].

[1] Department of Experimental and Clinical Biomedical Sciences “M. Serio”, University of Florence, Florence, Italy;

[2] Radiation Oncology Unit, Oncology Department, Azienda Ospedaliero Universitaria Careggi, Florence, Italy;

[3] Department of Radiation Oncology (Maastro), GROW School for Oncology and Developmental Biology, Maastricht University Medical Centre+, Maastricht, The Netherlands;

[4] Sheba Medical Center, Ramat Gan and Sackler School of Medicine, Tel-Aviv University, Tel-Aviv, Israel;

[5] Department of Radiation Oncology - Hospital Sírio-Libanês, São Paulo, Brazil;

[6] Latin American Cooperative Oncology Group (LACOG);

[7] Department of Radiation Oncology, HM Hospitales, Madrid, Spain;

[8] Department of Experimental Clinical Oncology, Department of Oncology, Danish Centre for Particle Therapy, Aarhus University Hospital, Aarhus, Denmark;

[9] Division of Cancer Sciences, School of Medical Sciences, Faculty of Biology, Medicine and Health, University of Manchester, Manchester, UK;

[10] The Christie NHS Foundation Trust, Manchester, UK;

[11] Department of Radiation Oncology, LMU Klinikum, Ludwig-Maximilians University Munich, Munich, Germany;

[12] School of Medicine, University of Keele, Keele, Staffordshire ST5 5BG, UK;

[13] Clinical Trials and Statistics Unit (ICR-CTSU), The Institute of Cancer Research, Sutton, London, UK;

[14] Division of Radiation Oncology, IEO, European Institute of Oncology, IRCCS, Milan, Italy;

[15] Department of Translational Medicine, University of Eastern Piedmont, Novara, Italy;

[16] Department of Radiation Oncology, “Maggiore della Carità” University Hospital, Novara, Italy;

[17] Department of Radiation Oncology, Faculty of Medicine and University Hospital Carl Gustav Carus, Technische Universität Dresden, Germany;

[18] OncoRay – National Center for Radiation Research in Oncology, Faculty of Medicine and University Hospital Carl Gustav Carus, Technische Universität Dresden and Helmholtz-Zentrum Dresden – Rossendorf, Germany;

[19] National Center for Tumor Diseases (NCT), Partner Site Dresden, German Cancer Research Center (DKFZ), Heidelberg; Faculty of Medicine and University Hospital Carl Gustav Carus, Technische Universität Dresden, Dresden, Germany, and Helmholtz-Zentrum Dresden – Rossendorf, Dresden, Germany;

[20] German Cancer Research Center (DKFZ), Heidelberg and German Cancer Consortium (DKTK), Dresden, Germany;

[21] Helmholtz-Zentrum Dresden – Rossendorf, Institute of Radiooncology, Germany;

[22] Trustee, Independent Cancer Patients' Voice, UK;

[23] Division of Radiation Oncology, Institute of Oncology Ljubljana, Ljubljana, Slovenia;

[24] Faculty of Medicine, University of Ljubljana, Ljubljana, Slovenia;

[25] Medical Physics Unit, Azienda Ospedaliero Universitaria Careggi, Florence, Italy;

[26] Department of Radiotherapy, Antoni van Leeuwenhoek-Netherlands Cancer Institute, Amsterdam, The Netherlands;

[27] Department of Oncology & Radiotherapy, Medical University of Gdańsk, Poland;

[28] College of the European School of Oncology Senior Faculty member;

[29] Department of Radiation Oncology, Iridium Netwerk, Antwerp 2610, Belgium;

[30] University of Antwerp, Faculty of Medicine and Health Sciences, Antwerp, Belgium;

[31] Department of Oncology, University of Cambridge, Cambridge, UK.

˚ equal contribution.

**Corresponding Author*

Icro Meattini, MD, Associate Professor

Department of Experimental and Clinical Biomedical Sciences "M. Serio", University of Florence

Viale Morgagni 50, 50134 – Florence, Italy

Tel: +39-055-7947264; fax +39-055-4379930; e-mail: icro.meattini@unifi.it

**European Society for Radiotherapy and Oncology (ESTRO) Advisory Committee in Radiation Oncology Practice (ACROP) consensus recommendations on patient selection and dose/fractionation for external beam radiation therapy in early breast cancer**

**Summary**

High-quality randomised clinical trials testing moderately fractionated breast radiation therapy have clearly demonstrated that local control and survival is at least as effective as with 2 Gy daily fractions with similar or reduced normal tissue toxicity. Less treatment visits are welcomed by patients and their families and reduced fractions produce substantial savings for healthcare systems.

Implementation of hypofractionation, however, has moved at a glacial pace. We have now reached an inflection point created by new evidence from the FAST-Forward 5-fraction randomised trial and catalysed by the need for the global radiation community to unite during the COVID-19 pandemic and rapidly re-think hypofractionation implementation.

The Consensus results state that moderately hypofractionated radiation therapy can be offered to any patient for breast, chest wall (with or without reconstruction) and nodal volumes. Ultra-fractionation (5-fractions) can also be offered for non-nodal breast/chest wall (without reconstruction) radiation therapy either as standard of care or within a randomised trial/prospective cohort.

This European Society for Radiotherapy and Oncology (ESTRO) Advisory Committee in Radiation Oncology Practice (ACROP) consensus is timely. Not only is it a pragmatic framework for radiation oncologists, but it provides a measured proposal for the path forward to influence policy makers and empower patients to ensure equity of access to evidence-based radiation therapy.

**Keywords**

Breast cancer; hypofractionation; partial breast irradiation; consensus; recommendations.

**Introduction**

The traditional dose/fractionation paradigms of radiation therapy for early-stage breast cancer, based on 50 Gy in 25 fractions over 5 weeks, are challenged. Over the last two decades, moderate hypofractionation (40-42.56 Gy in 15-16 fractions over 3 weeks) has been demonstrated to be at least as effective with respect to

local control and survival with similar, if not decreased, early and late normal tissue effects (NTE) as compared to conventionally fractionated whole breast irradiation (WBI) [1-5]. Moreover, recent data shows that ultra-hypofractionated WBI, delivered in 5 daily fractions to a total of 26 Gy, is non-inferior at 5-years in terms of local recurrence and provides lower acute and similar late NTE rates compared with a moderate hypofractionated schedule [3]. However, hypofractionation is still not used universally,[6,7] despite the abundance of level-1 evidence on thousands of breast cancer patients and long-term follow up supporting its use[1,2].

The European Society for Radiotherapy and Oncology (ESTRO) consensus recommendations clarified locoregional target volume delineation following breast conservation and mastectomy [8], in the setting of both postmastectomy radiation therapy after reconstruction [9] and partial breast irradiation (PBI) [10]. However, a lack of agreement persists in the radiation oncology community with respect to radiation dose/fractionation/volume selection in early-stage breast cancer.

A consensus is needed to harmonize expert opinions about hypofractionation, not only concerning local control, but also other important clinical endpoints such as side effects, health-related quality of life, and cosmesis to benefit the wide population of breast cancer patients. Consensus statements differ from guidelines, which are developed following a systematic review of the evidence, because they are produced by experts stating areas of agreement and disagreement on a topic via a specified methodology.

This ESTRO-Advisory Committee in Radiation Oncology Practice (ACROP) consensus addresses dose/fractionation for whole and partial breast, chest wall and regional nodal irradiation. The aim is to support equity of access for all patients to receive evidence-based breast external beam radiation therapy and identify remaining evidence gaps requiring international collaboration to design future research.

## Methods

*Consensus group*

A Core Group (CG) of the Consensus panel led by co-chairs (CC, IM, PP) was responsible for writing the protocol, consensus development, and drafting the manuscript. The Expert Panel (EP), including representatives from relevant clinical specialties and patient advocates, was identified by the Consensus CG and endorsed by both ESTRO-ACROP and ESTRO-National Societies Committee. The writing committee of the Consensus included both the CG and the EP (**Web-appendix, page 1**). Overall, twenty-six panellists were invited to reflect a diverse spectrum of opinions and to minimise potential biases inherent to recommendations; twenty-three panellists accepted the invitation. Recommendations were drafted by the CG in collaboration with the EP. The consensus process, including its three key phases, is reported in **Figure 1**.

*Consensus methods*

A modified Delphi strategy was adopted to provide a highly structured transparent process and obtain anonymous feedback [11], following a reproducible methodology [12]. The consensus process involved several iterations of independent anonymous voting on draft recommendations and subsequent revisions. This enabled participants to reassess their own judgments over time as recommendations were revised according to feedback received through the process. Quantitative data were collected to facilitate statistical analyses [13]. Rating of the recommendations was then performed by the writing committee. Agreement with each recommendation was rated using a five-point Likert scale, ranging from strongly disagree (Score 1) to strongly agree (Score 5), as higher score corresponds to a stronger agreement. A consensus was defined *a priori* as ≥75% participants indicating agreement (scores 4 and 5 combined) or disagreement (scores 1 and 2 combined) with a given recommendation (100% unanimous support; 90-99% strong support; 75-89% support). If consensus was not achieved, this was noted. Participants were invited to vote again, after discussion and adaptation/reformulation in the subsequent round on items that had not reached 75% or more agreement. For all statements, detailed results from the voting rounds were provided in the report. Any item that still did not reach a consensus after third voting round was excluded.

*Recommendation development and adoption*

We circulated surveys amongst all individual participants using the online survey tool Google Forms (anonymous). The panellists were reminded to base their responses exclusively on the available scientific evidence regardless of any potential influence related to personal/local/national practice. In round one, initial survey was sent out to the whole group together with a summary of available literature evidence (**Web-appendix, page 2 to 4**). Two investigators (CB, IM) consolidated and harmonised all the participants' responses. These were discussed by the CG and used to develop a second set of statements that was circulated to all participants in the second round of the Delphi process. After the second voting round and subsequent discussion of comments received by panellists, a third and final voting round was performed.

*Search strategy and selection criteria*

References for this Policy Review were identified through searches of PubMed with the search terms "breast cancer", "hypofractionation", "partial breast irradiation", and "fractionation" from 2002 until July, 2021. Articles were also identified through searches of the authors' own files. Only papers published in English were

reviewed. The final reference list was generated on the basis of originality and relevance to the broad scope of this Review.

## Results

### Key-topics

The CG identified the level-of-evidence for key-topics on patient selection and fractionation for external beam radiation therapy (EBRT) in early breast cancer (Q1/. “For each key-topic, what is the existing level-of-evidence?”; Q2/. “Do you think that a systematic literature’s review is needed?”). The CG concluded that a systematic literature review was only needed for the topic of PBI and fractionation. Since a meta-analysis on the topic is currently underway (data collecting phase) by the Early Breast Cancer Trialists' Collaborative Group (EBCTCG), the CG agreed that it would be inappropriate to duplicate this effort.

### First voting round

*Whole breast, nodal, and chest wall irradiation*

After the first voting round (23 respondents out of 23 panellists; 100%), consensus was reached for offering moderate hypofractionated WBI (40-42.56 Gy in 15-16 fractions over 3 weeks) regardless of age at breast cancer diagnosis (strong consensus 91.3%), pathological tumour stage (strong consensus 91.3%), breast cancer biology (strong consensus 91.3%), surgical margin status (unanimous consensus 100%), tumour bed boost indication (unanimous consensus 100%), breast size (strong consensus 91.3%), invasive or pre-invasive (DCIS) disease (strong consensus 91.3%), oncoplastic breast conserving surgery (strong consensus 91.3%), and use of systemic therapy (strong consensus 95.6%). Consensus was also reached for offering moderate hypofractionation for chest wall irradiation without breast reconstruction (strong consensus 95.6%), with reconstruction regardless of its timing and type of breast reconstruction (consensus 86.9%), and for regional nodal irradiation (consensus 82.6%). For ultra hypofractionated (5 fractions) WBI and chest wall irradiation a consensus was not reached.

*Partial breast irradiation*

After first voting (23 respondents out of 23 panellists; 100%), consensus was reached on the following features considered applicable to PBI: luminal-like subtype and small tumour sized ≤3 cm (strong consensus 91.3%), absence of lymph vascular space invasion (consensus 87%), non-lobular invasive carcinoma (consensus 87%), tumour grade 1-2 (strong consensus 91.3%), low to intermediate grade DCIS sized ≤2.5 cm with clear

surgical margins ≥3 mm (consensus 78.2%), age at diagnosis ≥ 50 years (consensus 87%), unicentric/unifocal lesion (unanimous consensus 100%). Uncertainties remained on the following: surgical margin status – no ink on tumour (support 65.2%); nodal status – node negative including isolated tumour cells (support 73.9%); no use of primary systemic therapy (support 73.9%). After first voting consensus was reached on the statement regarding the fact that "twice daily external beam PBI dose/fractionations, similar to those used in the RAPID trial, should not be offered" (consensus 86.9%). Conversely, a consensus was not reached on the following schedules: moderate hypofractionation 40 Gy in 15 fractions (69.6%), 30 Gy in 5 fractions (60.4%), 26 Gy in 5 fractions (65.2%).

Second and third voting rounds

After the second voting round (23 respondents out of 23 panellists; 100%), a wider consensus was obtained on ultra-hypofractionation (26 Gy in 5 fractions over one week) for WBI (consensus 86.9%) and chest wall irradiation without breast reconstruction (consensus 78.3%), selection criteria and suitable fractionation for PBI. After discussion of comments received by panellists on ultra-hypofractionation for chest wall irradiation after breast reconstruction (no consensus, 52.2%), a third voting round was required (21 respondents out of 23 panellists; 91.3%) and a consensus was obtained on a revised statement supporting 5 fractions for chest wall irradiation after breast reconstruction within a randomised controlled or prospective registration cohort trial (strong consensus 90.5%). Delphi voting agreement results detailed by round 1 to 3 is shown on **Web-appendix (page 5 to 9)**.

A final poll (more than one option allowed) requesting personal preference between (i) standard-of-care and (ii) randomised controlled trial/prospective registration cohort study was performed on ultra-hypofractionation for WBI and chest wall irradiation without reconstruction (17 respondents out of 23 panellists; 73.9%). Concerning WBI, panellists' preference was in favour of adopting ultra-hypofractionation as standard-of-care (82.4%) over randomised/prospective registration cohort studies (64.7%). Concerning chest wall irradiation without breast reconstruction both options obtained 76.5% (consensus) of preference.

Voting agreement and strength of consensus after three Delphi voting rounds are presented in **Panel 1** and the final consensus statements are summarized in **Panel 2**, reflecting panellists' collective analysis and evaluation of the best available evidence, as well as their expert opinion on a topic.

## Discussion

1. Whole breast irradiation

***Statement 1a. Moderate hypofractionated whole breast irradiation should be offered regardless of age at breast cancer diagnosis, pathological tumour stage, breast cancer biology, surgical margins status, tumour bed boost, breast size, invasive or pre-invasive (DCIS) disease, oncoplastic breast conserving surgery, and use of systemic therapy.***

Two pivotal trials, the Ontario Clinical Oncology Group (OCOG) trial [14] and UK START trial B [15], comparing moderate hypofractionation (40-42.5 Gy in 15-16 fractions over 3 weeks) with 50 Gy in 25 fractions over 5 weeks, showed comparable 5-year rates of local recurrence and NTE, with a statistically significant reduction in NTE for 40 Gy in 15 fractions over 3 weeks. Long-term results of these trials confirmed that moderate hypofractionated WBI is both safe and effective [1,2,16], slowly becoming an international standard-of-care [17]. In addition, several systematic reviews and meta-analyses on hypofractionation have been published over the last decade, all demonstrating the effectiveness and safety of moderate hypofractionation as compared to 2 Gy daily fractionated schedules [18-21]. The recent Danish Breast Cancer Cooperative Group (DBCG) HYPO trial (median follow up 7.3 years) also supports 40 Gy in 15 fractions over 3 weeks as a standard for WBI [5]. Several studies reported significantly less radiation-related acute toxicity (i.e., erythema, desquamation, fatigue) with moderate hypofractionation as compared to conventional schedule [1,2,4,5,16,22,23], reinforcing the radiobiological basis of acute reacting tissue higher sensitivity to total dose rather than dose per fraction [24]. None of the above-mentioned trials identified a specific subgroup of patients for whom hypofractionation could be responsible for a worse outcome in terms of neither efficacy nor NTE, including age, use of systemic therapies (i.e., chemotherapy, endocrine therapy, anti-Human Epidermal growth factor Receptor 2 [HER2] therapy) [5,25], as well as tumour grade and molecular subtype [26,27]. DCIS of the breast was scarcely represented in main trials, although available evidence showed no difference in terms of local recurrence rate at 5 years [5,28].

***Statement 1b. Ultra-hypofractionated (26 Gy in 5 fractions) whole breast irradiation can be offered as (i) standard-of-care or (ii) within a randomised controlled trial or prospective registration cohort.***

The FAST-Forward randomised trial (n=4096) showed that ultra-hypofractionation (26 Gy in 5 daily fractions) leads to non-inferior local control rates and similar adverse event profile as compared to 40 Gy in 15 fractions over 3 weeks [3]. The trial evaluated 27 Gy in 5 fractions of 5.4 Gy or 26 Gy in 5 fractions of 5.2 Gy both given daily over 1 week in women with early invasive breast cancer after breast conserving surgery or mastectomy [3]. At a median follow up of 6 years, both 5-fraction regimens were shown to be non-inferior in terms of local recurrence as compared to 40 Gy in 15 fractions: HR versus 40 Gy in 15 fractions of 0.86 (95% CI 0.51 to 1.44) for 27 Gy and 0.67 (95% CI 0.38 to 1.16) for 26 Gy in five fractions. Late NTE as assessed by clinicians,

patients and photographs, were similar for 26 Gy (HR 1.12, 95% CI 0.94 to 1.34; p=0.20) but worse for 27 Gy compared to 40 Gy at 5 years (HR 1.55, 95% CI 1.32 to 1.83; p<0.0001). Breast induration outside the tumour bed was the only statistically significant (at p<0.0001) worse NTE result for 26Gy in 5-fractions. However, the clinical significance for this endpoint is debatable with the observed 5-year rates of moderate/marked events being only 1.9% in 26 Gy and 0.1% in 40 Gy.

The smaller FAST trial randomised 915 women aged more than 50 years with early breast cancer (pT1-2 N0), after breast conserving surgery to 50 Gy in 25 fractions over 5 weeks or two hypofractionated schedules of 30/28.5 Gy in 5 fractions of 6/5.7 Gy once weekly delivered over 5 weeks [4]. NTE endpoints were used as outcome measures. At a 9.9-year median follow-up, all physician assessments showed no statistical difference between 28.5 Gy and 50 Gy. Five- and 10-year cross-sectional results were not different, although cumulative incidence rates of any marked/moderate NTE and breast induration were higher for 28.5 as compared to 50 Gy. Local recurrence rates were overall low and similar between arms. The main hypofractionation studies are summarized in **Panel 3**.

2. Chest wall irradiation

***Statement 2a. Moderate hypofractionation can be offered for chest wall irradiation without breast reconstruction.***

***Statement 2b. Moderate hypofractionation can be offered for chest wall irradiation regardless of time and type of breast reconstruction.***

Moderate hypofractionation for chest wall irradiation is under-represented within randomised trials. Mastectomy was not included in the Ontario trial and represented less than 10% of patients in the START B trial. Though it has been established as standard of care in some countries for many years, the overall uptake of moderate hypofractionation for chest wall irradiation remains around 50% in Europe [29]. There is no biological reason to assume that the efficacy and toxicity profile observed after breast conserving surgery does not apply to postmastectomy irradiation [28]. Wang and colleagues recently reported the results of a single-centre trial of postmastectomy RT on 810 women with primary T3-4 tumours or at least 4 positive axillary nodes randomized to 43.5 Gy in 15 fractions or 50 Gy in 25 fractions both to the chest wall and level 3-4 axillary nodal regions [31]. At around 5 years of median follow-up, the risk of locoregional recurrence was similar between treatment arms and no significant increase in late NTE was observed. The only significant difference described was the reduced severity of acute skin toxicity in patients treated with hypofractionation, which is reassuringly consistent with recent observations [32-34]. Further evidence is awaited from other groups, which are conducting

clinical trials to investigate this clinical setting, including in France (NCT03127995), the USA (NCT02700386, NCT02958774), Denmark (NCT02384733), and Egypt (NCT02690636).

There are no large randomised trials testing moderate hypofractionation post mastectomy radiation therapy in the setting of breast reconstruction. Small, non-randomised series suggest that late NTE and capsular contracture rates are similar to those obtained with 2 Gy daily fractionation [35]. The lower equivalent dose in 2 Gy fractions with 40 Gy in 15 fractions compared with 50 Gy in 25 fractions, would in fact favour moderately hypofractionated radiation therapy [35]. This dose/fractionation has been a standard of care for all types of breast reconstruction for some years in many countries (e.g. UK NICE guidance 2018: https://www.nice.org.uk/guidance/ng101/chapter/Recommendations#radiotherapy).

***Statement 2c. Ultra-hypofractionation (26 Gy in 5 fractions) for chest wall irradiation without breast reconstruction can be offered as (i) standard-of-care or (ii) within a randomised controlled trial or prospective registration cohort.***

Relative mastectomy proportions within FAST-Forward were as follows: 6.7% (n=91), 6.5% (n=89), and 6.1% (n=84) in the 40 Gy, 27 Gy, and 26 Gy groups, respectively. One local recurrence was observed in the 40 Gy and none in the 173 patients in the 5-fraction arms. The 2021 (UK) Royal College of Radiologists' Consensus Statements Programme reached a consensus on offering 26 Gy in 5 fractions over one week for chest wall irradiation [34].

***Statement 2d. Ultra-hypofractionation (26 Gy in 5 fractions) for chest wall irradiation after breast reconstruction can be offered within a randomised controlled trial or prospective registration cohort.***

Immediate reconstruction rates within FAST-Forward trial were <1% across all groups with only 10 patients receiving immediate implant-based reconstruction [3]. Although it was noted that there was no biological reason why patients with an immediate reconstruction should have higher risk of NTE toxicity, 26 Gy in 5-fraction schedule for chest wall irradiation following breast reconstruction requires further clinical evidence.

3. Nodal irradiation

***Statement 3a. Moderate hypofractionation should be offered for nodal irradiation.***

A minority of patients (<15%) enrolled in START trials using moderate hypofractionation received nodal irradiation [25]. There have been no safety concerns either in terms of cancer control or NTE and 40 Gy in 15 fractions over 3 weeks has been the UK standard of care for nodal RT for over a decade and in most of the

Netherlands' centres 42.56 Gy in 16 fractions was used until they recently adapted to 40 Gy in 15 fractions. All patients treated in the Beijing trial (43.5 Gy in 15 versus 50 Gy in 25 fractions) received nodal irradiation, reporting equivalent late NTE rates [31]. The UK IMPORT High trial will report on 5-year results in 2021 and will also include a proportion of patients receiving moderately hypofractionated nodal RT [37]. The DBCG RT Skagen trial 1 (NCT02384733) completed accrual July 2021 with 2963 high-risk patients randomized between 50 Gy in 25 fractions versus 40 Gy in 15 fractions for loco-regional RT based on the ESTRO consensus for target volume definition, and first results are expected during 2022 [38].

***Statement 3b. Ultra-hypofractionation (26 Gy in 5 fractions) should not be offered for nodal irradiation until ongoing trials results are reported.***

Nodal irradiation was not included in the FAST-Forward main trial cohort [3], and the FAST-Forward nodal sub-study is not reported as follow up is not mature (expected 2022). Therefore, 5-fraction nodal radiation therapy cannot yet be considered a current standard of care.

4. External beam partial breast irradiation: selection of patients

***Statement 4. Low risk-features suitable for partial breast irradiation are: luminal-like subtypes small tumour (≤3 cm), absence of lymph vascular space invasion, non-lobular invasive carcinoma, tumour grade 1-2, low to intermediate grade DCIS (sized ≤2.5 cm with clear surgical margins ≥3 mm), age at diagnosis 50 years or more, unicentric/unifocal lesion, clear surgical margins (>2 mm), node negative (including isolated tumour cells), and no use of primary systemic therapy/neoadjuvant chemotherapy.***

Few systematic reviews and meta-analyses were conducted to compare the effectiveness of distinct PBI approaches with WBI for the treatment of patients with breast cancer [39-42], showing that the balance between benefit and risk of PBI appears optimal for low-risk women [43,44]. Several phase 3 trials on external beam PBI versus WBI showed non inferior local control and comparable rates of distant metastases, breast cancer specific and overall survival in selected patients at low risk of recurrence [45-47]. Reports on late NTE show differing results or are unreported. The crucial role of patient selection for PBI was highlighted by the ELIOT trial, starting before the definition of the ASTRO and GEC-ESTRO guidelines, where there was a significant increase in the rate of local relapse in the PBI arm, due to enrolment of patients with high-risk tumours (>25% patients had lymph node positive disease and >20% had G3 tumours) [48-51], while subgroup analyses according to the GEC-ESTRO and the ASTRO criteria showed no differences for PBI compared to WBI in the low-risk groups [52,53]. Therefore, PBI should be considered for those patients with low-risk disease when treating outside

the setting of a clinical trial [54]. Overall, the PBI guidelines are similar albeit with some differences [55-57]. Main PBI studies are summarized in **Panel 4**.

5. External beam partial breast irradiation: dose and fractionation

***Statement 5a. Moderate hypofractionation (40 Gy in 15 fractions) and ultra-hypofractionation (26 to 30 Gy in 5 fractions) represent acceptable schedules for external beam partial breast irradiation.***

PBI may be delivered using a variety of techniques including intraoperative radiation therapy [48], brachytherapy [58,59], and EBRT [45-47,60]. For intraoperative radiation therapy [61] and brachytherapy [10] PBI techniques, the respective ESTRO-ACROP guidelines should be followed. Therefore, this consensus about fractionation schedules focused on exclusively trials using EBRT techniques. Trials reporting on PBI delivered using EBRT include APBI-IMRT Florence [45], UK IMPORT LOW [47], RAPID [46], and NSABP B-39/RTOG 0413 [60]. The APBI-IMRT Florence randomised trial on 520 patients used 30 Gy in 5 fractions over 2 weeks for PBI versus WBI 50 Gy in 25 fractions plus a tumour bed boost of 10 Gy in 5 fractions [45]. At 10-years, local recurrence rates were 3.7% and 2.5% (HR 1.56, 95% CI 0.55 to 4.37; p=0.40) in the PBI and WBI groups respectively, with reduced toxicity (both acute and late) and improved cosmesis in the PBI group. The UK IMPORT LOW randomised trial on 2018 women used moderate hypofractionation 40 Gy in 15 fractions over 3 weeks for PBI using simple 'field in field' IMRT [47]. At a median follow-up of 6 years, local relapse rates were 1.1% (95% CI 0.5 to 2.3) and 0.5% (95% CI 0.2 to 1.4) in the WBI and PBI groups, respectively. Of note, the risk of contralateral breast cancer was 2% at 5 years. Late toxicity was either similar or significantly less (beast appearance and breast hardness) in the PBI group as compared to the WBI group [62]. The FAST-Forward trial (26 Gy in 5 fractions WBI) [3] was designed in parallel with the UK IMPORT LOW (40 Gy in 15 fractions PBI) [47], with the same dose/fractionation for the control group (40 Gy in 15 fractions WBI). The FAST-Forward trial showed non-inferiority with 40 Gy in 15 fractions for efficacy and similar toxicity, whilst the UK IMPORT LOW showed non-inferiority with 40 Gy in 15 fractions for efficacy and reduced toxicity.

The RAPID randomised trial used 38.5 Gy in 10 fractions twice daily over one week [46]. The trial met the pre-specified non-inferiority assumption for the primary endpoint (to exclude HR >2.02 calculated from 5-year estimated recurrence rates). Conversely, the NSABP B-39/RTOG 0413 trial randomly assigned 4216 women to receive either PBI using EBRT or brachytherapy technique (38.5 Gy with EBRT or 34 Gy for brachytherapy in 10 twice-daily fractions over one week) or WBI with or without a tumour bed boost [60]. At 10 years, the local recurrence rate was 4.6% for PBI and 3.9% for WBI (HR 1.22, 90% CI 0.94 to 1.58), which are both low, but did not meet their prespecified conditions for equivalence (to exclude HR ≤0.677 or ≥1.50 irrespective of time

point). Clinically, the HR and associated CI are similar between the two trials and any difference in interpretation is strictly related to statistical design [63].

Given this pre-planned strategy and the non-feasibility for a further 5- against 10- or 15-fraction PBI trial due to vast numbers needed given the extremely low event rate in this very low risk population, the UK Royal College of Radiologists breast consensus update in 2020 supported offering 26 Gy in 5 fractions for PBI as standard [36]. In addition, equipoise is lacking to support a 26 Gy in 5 fraction PBI trial given the efficacy and very low rates of NTE with WBI within the FAST-Forward trial. Furthermore, the Florence trial already supports the use of 5-fraction PBI to a slightly higher dose with low rates of NTE [45].

***Statement 5b. Twice-daily external beam partial breast irradiation dose/fractionations similar to those used in the RAPID trial should not be offered.***

In the RAPID trial [46], cosmetic outcome was significantly worse in patients receiving PBI and the authors do not recommend this twice-daily fractionation. This could be related to the high volume of breast receiving 50% of the prescribed dose and to the twice-daily fractionation where the equivalent dose in 2 Gy per fraction is around 53 Gy; however, it may in fact be as high as 65 Gy if incomplete repair between fractions is considered [30]. The NSABP B-39/RTOG 0413 study reported similar toxicity between the treatment groups although published detail was very limited and a further publication focusing on late NTE is expected [60]. Therefore, caution is advised with twice-daily PBI until the full published reports of the NSABP B-39/RTOG 0413 study NTE results and/or the IRMA randomised trial (NCT01803958) are available.

**Conclusions and future directions**

Moderate hypofractionation for whole breast, chest wall, and nodal irradiation with or without breast reconstruction has been proven to be non-inferior, at least equally safe, and more cost-effective as compared to conventional fractionation [64]. The 26 Gy in 5-fraction schedule can be used as an alternative for breast and chest wall irradiation. Subgroup analyses comparing clinician-assessed moderate or marked adverse effect for 26 Gy versus 40 Gy show no evidence of differential effects according to age, breast size, surgical deficit, tumour bed boost, or adjuvant chemotherapy [65]. Further publications from prospective cohort studies and randomised trials that add to the experience of using 5-fraction will be important, especially for under-represented patient groups such as breast reconstruction. As with all UK breast radiation therapy studies, the FAST Forward trial will continue follow up for 10 years after completion of treatment, as this represents excellent practice whereby optimal information is gained from every patient within a clinical trial. It is clear that

the currently extremely low rates of NTE will increase over time as seen in all breast radiation therapy trials, but these will increase at the same pace in all groups of the study. This has been demonstrated elegantly by the long-term results of the moderately hypofractionated START B trial [25] and more recently, the ultra-fractionated FAST trial [4], whereby the HR for late NTE in all study groups remain remarkedly similar at both 5 and 10 years.

Well-defined selection criteria for patient's eligibility to receive PBI exist and should be routinely followed. Indeed, an appropriate selection of patients allows for equivalent disease control and comparable, if not improved, safety profile as compared to WBI. Once-daily schedules, as per main phase 3 randomized trials, should be favoured as compared to twice-daily schedules.

All these high-level findings in early breast cancer call for an important, even urgent in regions with insufficient radiation oncology coverage, adaptation of routine practice now as a duty of an international community. This consensus aims to translate new evidence more quickly than in the past into routine daily practice. This is likely to lead to clear benefits for both individuals and their families (socioeconomic and also related to a decreased acute toxicity, an earlier recovery, and a subsequent fast back to "normal"). The favourable impact of shorter/less toxic schedule implementation will also add benefits for radiation therapy centres and national health services, allowing for re-distribution of limited resource, shortening of waiting times, and overall improvement of departments' capacity.

However, we are aware of the existing barriers to implementation of new practice: lack of experience in hypofractionation, minimal resources for quality assurance in radiation therapy and inadequate support to change. Another important barrier is reimbursement policies: reimbursement per fraction, and not for the whole course of radiation, is common in many countries and creates a disincentive to change due to loss of income to institutions or individuals [66]. This issue is even more crucial in low and middle-income countries, as the lack of radiation therapy infrastructure means that thousands of patients have no access to any irradiation and those that could have access cannot afford to travel daily/stay away from home for extended periods [35,67]. This is also important in wealthy countries, where patients from lower socioeconomic backgrounds and non-Caucasian are less likely to receive hypofractionation [68]. Therefore, we need to promote the re-examination of current reimbursement systems to facilitate equity of access for all patients [64,66].

As with any treatment, the benefits, risks and uncertainties should be discussed and a shared-decision reached with the patient, accounting for his/her expectations, warranting equity of access to evidenced-based breast irradiation. This patient-centred approach is facilitated when a framework of national consensus statements exists (e.g., The Royal College of Radiologists' Consensus Statements Programme) [36]. Indeed, consensus

embeds patient and public involvement and engagement, providing a driver for further patient pressure for change.

Overall, this ESTRO-ACROP consensus aims to present a significant contribution to breaking down the above-mentioned existing barriers, giving a practical tool to inspire local/national breast radiation therapy protocols and to facilitate new collaborative and meaningful research in areas requiring further evidence (e.g., 26 Gy in 5-fraction schedule for chest wall irradiation following breast reconstruction). We aim to promote education, highlighting existing evidence and documented benefit for patients, providing sense of community, support and collective impetus for change, while opening dialogue for candid discussion about reimbursement at a national/international policy level.

**Authors' Contributions**

IM, PP, CC, CB contributed to conceptualisation, data curation, formal analysis, investigation, methodology, project administration, supervision, validation, writing – original draft, and writing – review & editing. LB, OKP, AM, GNM, BVO contributed to conceptualisation, data curation, formal analysis, investigation, validation, writing – original draft, and writing – review & editing. All authors contributed to the statements voting, the interpretation of data, and writing and approval of the manuscript.

**Role of funding source**

None funding sources disclosed. All authors had full access to the full data in the study and accept responsibility to submit for publication.

**Declaration of interests**

IM declares advisory boards supported by Eli Lilly, Novartis, Istituto Gentili, Roche, Pfizer, Ipsen, and Pierre Fabre. MCA received grant supported by the charity Cancer Research UK. CB declares honoraria supported by C-RAD and Elekta. PP is medical advisor of Sordina IORT Technologies.

**Acknowledgments**

CEC is funded by the National Institute of Health Research (NIHR) and supported by the NIHR Cambridge Biomedical Research Centre; the views expressed are those of the author and not necessarily those of the NIHR or the Department of Health and Social Care.

**References**


1. Haviland JS, Owen JR, Dewar JA, et al. The UK Standardisation of Breast Radiotherapy (START) trials of radiotherapy hypofractionation for treatment of early breast cancer: 10-year follow-up results of two randomised controlled trials. *Lancet Oncol* 2013; **14**(11): 1086-94.

2. Whelan TJ, Pignol JP, Levine MN, et al. Long-term results of hypofractionated radiation therapy for breast cancer. *N Engl J Med* 2010; **362**(6): 513-20.

3. Murray Brunt A, Haviland JS, Wheatley DA, et al. Hypofractionated breast radiotherapy for 1 week versus 3 weeks (FAST-Forward): 5-year efficacy and late normal tissue effects results from a multicentre, non-inferiority, randomised, phase 3 trial. *Lancet* 2020; **395**(10237): 1613-26.

4. Brunt AM, Haviland JS, Sydenham M, et al. Ten-Year Results of FAST: A Randomized Controlled Trial of 5-Fraction Whole-Breast Radiotherapy for Early Breast Cancer. *J Clin Oncol* 2020; **38**(28): 3261-72.

5. Offersen BV, Alsner J, Nielsen HM, et al. Hypofractionated Versus Standard Fractionated Radiotherapy in Patients With Early Breast Cancer or Ductal Carcinoma In Situ in a Randomized Phase III Trial: The DBCG HYPO Trial. *J Clin Oncol* 2020; **38**(31): 3615-25.

6. Venigalla S, Guttmann DM, Jain V, Sharma S, Freedman GM, Shabason JE. Trends and Patterns of Utilization of Hypofractionated Postmastectomy Radiotherapy: A National Cancer Database Analysis. *Clin Breast Cancer* 2018; **18**(5): e899-e908.

7. Boero IJ, Gillespie EF, Hou J, et al. The Impact of Radiation Oncologists on the Early Adoption of Hypofractionated Radiation Therapy for Early-Stage Breast Cancer. *Int J Radiat Oncol Biol Phys* 2017; **97**(3): 571-80.

8. Offersen BV, Boersma LJ, Kirkove C, et al. ESTRO consensus guideline on target volume delineation for elective radiation therapy of early stage breast cancer. *Radiother Oncol* 2015; **114**(1): 3-10.

9. Kaidar-Person O, Vrou Offersen B, Hol S, et al. ESTRO ACROP consensus guideline for target volume delineation in the setting of postmastectomy radiation therapy after implant-based immediate reconstruction for early stage breast cancer. *Radiother Oncol* 2019; **137**: 159-66.

10. Strnad V, Major T, Polgar C, et al. ESTRO-ACROP guideline: Interstitial multi-catheter breast brachytherapy as Accelerated Partial Breast Irradiation alone or as boost - GEC-ESTRO Breast Cancer Working Group practical recommendations. *Radiother Oncol* 2018; **128**(3): 411-20.

11. Murphy MK, Black NA, Lamping DL, et al. Consensus development methods, and their use in clinical guideline development. *Health Technol Assess* 1998; **2**(3): i-iv, 1-88.

12. Loblaw DA, Prestrud AA, Somerfield MR, et al. American Society of Clinical Oncology Clinical Practice Guidelines: formal systematic review-based consensus methodology. *J Clin Oncol* 2012; **30**(25): 3136-40.

13. Hsu CS, B. A. The Delphi Technique: Making Sense of Consensus. *Practical Assessment, Research, and Evaluation* 2007; **12**: 1-8.

14. Whelan T, MacKenzie R, Julian J, et al. Randomized trial of breast irradiation schedules after lumpectomy for women with lymph node-negative breast cancer. *J Natl Cancer Inst* 2002; **94**(15): 1143-50.

15. Group ST, Bentzen SM, Agrawal RK, et al. The UK Standardisation of Breast Radiotherapy (START) Trial B of radiotherapy hypofractionation for treatment of early breast cancer: a randomised trial. *Lancet* 2008; **371**(9618): 1098-107.

16. Brunt AM, Wheatley D, Yarnold J, et al. Acute skin toxicity associated with a 1-week schedule of whole breast radiotherapy compared with a standard 3-week regimen delivered in the UK FAST-Forward Trial. *Radiother Oncol* 2016; **120**(1): 114-8.

17. Smith BD, Bellon JR, Blitzblau R, et al. Radiation therapy for the whole breast: Executive summary of an American Society for Radiation Oncology (ASTRO) evidence-based guideline. *Pract Radiat Oncol* 2018; **8**(3): 145-52.

18. Valle LF, Agarwal S, Bickel KE, Herchek HA, Nalepinski DC, Kapadia NS. Hypofractionated whole breast radiotherapy in breast conservation for early-stage breast cancer: a systematic review and meta-analysis of randomized trials. *Breast Cancer Res Treat* 2017; **162**(3): 409-17.

19. Andrade TRM, Fonseca MCM, Segreto HRC, Segreto RA, Martella E, Nazario ACP. Meta-analysis of long-term efficacy and safety of hypofractionated radiotherapy in the treatment of early breast cancer. *Breast* 2019; **48**: 24-31.

20. Hickey BE, James ML, Lehman M, et al. Fraction size in radiation therapy for breast conservation in early breast cancer. *Cochrane Database Syst Rev* 2016; **7**: CD003860.

21. Marta GN, Coles C, Kaidar-Person O, et al. The use of moderately hypofractionated post-operative radiation therapy for breast cancer in clinical practice: A critical review. *Crit Rev Oncol Hematol* 2020; **156**: 103090.

22. Shaitelman SF, Schlembach PJ, Arzu I, et al. Acute and Short-term Toxic Effects of Conventionally Fractionated vs Hypofractionated Whole-Breast Irradiation: A Randomized Clinical Trial. *JAMA Oncol* 2015; **1**(7): 931-41.

23. Wang SL, Fang H, Hu C, et al. Hypofractionated Versus Conventional Fractionated Radiotherapy After Breast-Conserving Surgery in the Modern Treatment Era: A Multicenter, Randomized Controlled Trial From China. *J Clin Oncol* 2020; **38**(31): 3604-14.

24. Fowler JF. The linear-quadratic formula and progress in fractionated radiotherapy. *Br J Radiol* 1989; **62**(740): 679-94.

25. Haviland JS, Mannino M, Griffin C, et al. Late normal tissue effects in the arm and shoulder following lymphatic radiotherapy: Results from the UK START (Standardisation of Breast Radiotherapy) trials. *Radiother Oncol* 2018; **126**(1): 155-62.

26. Bane AL, Whelan TJ, Pond GR, et al. Tumor factors predictive of response to hypofractionated radiotherapy in a randomized trial following breast conserving therapy. *Ann Oncol* 2014; **25**(5): 992-8.

27. Koulis TA, Nichol AM, Truong PT, et al. Hypofractionated Adjuvant Radiation Therapy Is Effective for Patients With Lymph Node-Positive Breast Cancer: A Population-Based Analysis. *Int J Radiat Oncol Biol Phys* 2020; **108**(5): 1150-8.

28. King MT, Link EK, Whelan TJ, et al. Quality of life after breast-conserving therapy and adjuvant radiotherapy for non-low-risk ductal carcinoma in situ (BIG 3-07/TROG 07.01): 2-year results of a randomised, controlled, phase 3 trial. *Lancet Oncol* 2020; **21**(5): 685-98.

29. Ratosa I, Chirila ME, Steinacher M, et al. Hypofractionated radiation therapy for breast cancer: Preferences amongst radiation oncologists in Europe - Results from an international survey. *Radiother Oncol* 2020; **155**: 17-26.

30. Yarnold J, Bentzen SM, Coles C, Haviland J. Hypofractionated whole-breast radiotherapy for women with early breast cancer: myths and realities. *Int J Radiat Oncol Biol Phys* 2011; **79**(1): 1-9.

31. Wang SL, Fang H, Song YW, et al. Hypofractionated versus conventional fractionated postmastectomy radiotherapy for patients with high-risk breast cancer: a randomised, non-inferiority, open-label, phase 3 trial. *Lancet Oncol* 2019; **20**(3): 352-60.

32. Jagsi R, Griffith KA, Boike TP, et al. Differences in the Acute Toxic Effects of Breast Radiotherapy by Fractionation Schedule: Comparative Analysis of Physician-Assessed and Patient-Reported Outcomes in a Large Multicenter Cohort. *JAMA Oncol* 2015; **1**(7): 918-30.

33. Sayan M, Yehia ZA, Ohri N, Haffty BG. Hypofractionated Postmastectomy Radiation Therapy. *Adv Radiat Oncol* 2021; **6**(1): 100618.

34. Liu L, Yang Y, Guo Q, et al. Comparing hypofractionated to conventional fractionated radiotherapy in postmastectomy breast cancer: a meta-analysis and systematic review. *Radiat Oncol* 2020; **15**(1): 17.

35. Marta GN, Poortmans P. Moderately hypofractionated breast radiation therapy: is more evidence needed? *Lancet Oncol* 2019; **20**(5): e226.

36. Lewis P, Brunt AM, Coles C, et al. Moving Forward Fast with FAST-Forward. *Clin Oncol (R Coll Radiol)* 2021.

37. Coles C, Griffin C, Kirby A, et al. Abstract GS4-05: Dose escalated simultaneous integrated boost radiotherapy for women treated by breast conservation surgery for early breast cancer: 3-year adverse effects in the IMPORT HIGH trial (CRUK/06/003). *Cancer Research* 2019; **79**(4 Supplement): GS4-05-GS4-.

38. Francolini G, Thomsen MS, Yates ES, et al. Quality assessment of delineation and dose planning of early breast cancer patients included in the randomized Skagen Trial 1. *Radiother Oncol* 2017; **123**(2): 282-7.

39. Lv Y, He L, Wang C, Zhang L, Zhang B, Song Y. A systematic review of clinical outcomes and radiotherapy-associated toxicity in multicatheter accelerated partial breast irradiation. *Medicine (Baltimore)* 2019; **98**(6): e14407.

40. Marta GN, Barrett J, Porfirio GJM, et al. Effectiveness of different accelerated partial breast irradiation techniques for the treatment of breast cancer patients: Systematic review using indirect comparisons of randomized clinical trials. *Rep Pract Oncol Radiother* 2019; **24**(2): 165-74.

41. Viani GA, Arruda CV, Faustino AC, De Fendi LI. Partial-breast irradiation versus whole-breast radiotherapy for early breast cancer: A systematic review and update meta-analysis. *Brachytherapy* 2020; **19**(4): 491-8.

42. Hickey BE, Lehman M, Francis DP, See AM. Partial breast irradiation for early breast cancer. *Cochrane Database Syst Rev* 2016; **7**: CD007077.

43. Korzets Y, Fyles A, Shepshelovich D, Amir E, Goldvaser H. Toxicity and clinical outcomes of partial breast irradiation compared to whole breast irradiation for early-stage breast cancer: a systematic review and meta-analysis. *Breast Cancer Res Treat* 2019; **175**(3): 531-45.

44. Tagliaferri L, Lancellotta V, Colloca G, et al. Could a Personalized Strategy Using Accelerated Partial Breast Irradiation be an Advantage for Elderly Patients? A Systematic Review of the Literature and Multidisciplinary Opinion. *J Oncol* 2020; **2020**: 3928976.

45. Meattini I, Marrazzo L, Saieva C, et al. Accelerated Partial-Breast Irradiation Compared With Whole-Breast Irradiation for Early Breast Cancer: Long-Term Results of the Randomized Phase III APBI-IMRT-Florence Trial. *J Clin Oncol* 2020; **38**(35): 4175-83.

46. Whelan TJ, Julian JA, Berrang TS, et al. External beam accelerated partial breast irradiation versus whole breast irradiation after breast conserving surgery in women with ductal carcinoma in situ and node-negative breast cancer (RAPID): a randomised controlled trial. *Lancet* 2019; **394**(10215): 2165-72.

47. Coles CE, Griffin CL, Kirby AM, et al. Partial-breast radiotherapy after breast conservation surgery for patients with early breast cancer (UK IMPORT LOW trial): 5-year results from a multicentre, randomised, controlled, phase 3, non-inferiority trial. *Lancet* 2017; **390**(10099): 1048-60.

48. Veronesi U, Orecchia R, Maisonneuve P, et al. Intraoperative radiotherapy versus external radiotherapy for early breast cancer (ELIOT): a randomised controlled equivalence trial. *Lancet Oncol* 2013; **14**(13): 1269-77.

49. Orecchia R, Veronesi U, Maisonneuve P, et al. Intraoperative irradiation for early breast cancer (ELIOT): long-term recurrence and survival outcomes from a single-centre, randomised, phase 3 equivalence trial. *Lancet Oncol* 2021; **22**(5): 597-608.

50. Kaidar-Person O, Poortmans P. Partial breast irradiation with intraoperative radiotherapy in the ELIOT trial. *Lancet Oncol* 2021; **22**(7): e294.

51. Marta GN, Meattini I. Partial breast irradiation with intraoperative radiotherapy in the ELIOT trial. *Lancet Oncol* 2021; **22**(7): e297.

52. Leonardi MC, Maisonneuve P, Mastropasqua MG, et al. How do the ASTRO consensus statement guidelines for the application of accelerated partial breast irradiation fit intraoperative radiotherapy? A retrospective analysis of patients treated at the European Institute of Oncology. *Int J Radiat Oncol Biol Phys* 2012; **83**(3): 806-13.

53. Leonardi MC, Maisonneuve P, Mastropasqua MG, et al. Accelerated partial breast irradiation with intraoperative electrons: using GEC-ESTRO recommendations as guidance for patient selection. *Radiother Oncol* 2013; **106**(1): 21-7.

54. Kaidar-Person O, Meattini I, Zippel D, Poortmans P. Apples and oranges: comparing partial breast irradiation techniques. *Rep Pract Oncol Radiother* 2020; **25**(5): 780-2.

55. Polgar C, Van Limbergen E, Potter R, et al. Patient selection for accelerated partial-breast irradiation (APBI) after breast-conserving surgery: recommendations of the Groupe Europeen de Curietherapie-European Society for Therapeutic Radiology and Oncology (GEC-ESTRO) breast cancer working group based on clinical evidence (2009). *Radiother Oncol* 2010; **94**(3): 264-73.

56. Correa C, Harris EE, Leonardi MC, et al. Accelerated Partial Breast Irradiation: Executive summary for the update of an ASTRO Evidence-Based Consensus Statement. *Pract Radiat Oncol* 2017; **7**(2): 73-9.

57. Bloomfield DJ, Core Group facilitated by The Royal College of R. Development of Postoperative Radiotherapy for Breast Cancer: UK Consensus Statements - a Model of Patient, Clinical and Commissioner Engagement? *Clin Oncol (R Coll Radiol)* 2017; **29**(10): 639-41.

58. Polgar C, Ott OJ, Hildebrandt G, et al. Late side-effects and cosmetic results of accelerated partial breast irradiation with interstitial brachytherapy versus whole-breast irradiation after breast-conserving surgery for low-risk invasive and in-situ carcinoma of the female breast: 5-year results of a randomised, controlled, phase 3 trial. *Lancet Oncol* 2017; **18**(2): 259-68.

59. Strnad V, Ott OJ, Hildebrandt G, et al. 5-year results of accelerated partial breast irradiation using sole interstitial multicatheter brachytherapy versus whole-breast irradiation with boost after breast-conserving surgery for low-risk invasive and in-situ carcinoma of the female breast: a randomised, phase 3, non-inferiority trial. *Lancet* 2016; **387**(10015): 229-38.

60. Vicini FA, Cecchini RS, White JR, et al. Long-term primary results of accelerated partial breast irradiation after breast-conserving surgery for early-stage breast cancer: a randomised, phase 3, equivalence trial. *Lancet* 2019; **394**(10215): 2155-64.

61. Fastner G, Gaisberger C, Kaiser J, et al. ESTRO IORT Task Force/ACROP recommendations for intraoperative radiation therapy with electrons (IOERT) in breast cancer. *Radiother Oncol* 2020; **149**: 150-7.

62. Bhattacharya IS, Haviland JS, Kirby AM, et al. Patient-Reported Outcomes Over 5 Years After Whole- or Partial-Breast Radiotherapy: Longitudinal Analysis of the IMPORT LOW (CRUK/06/003) Phase III Randomized Controlled Trial. *J Clin Oncol* 2019; **37**(4): 305-17.

63. Coles CE. Another piece in the jigsaw of accelerated partial breast irradiation. *Lancet Oncol* 2017; **18**(2): 168-9.

64. Cardoso F, MacNeill F, Penault-Llorca F, et al. Why is appropriate healthcare inaccessible for many European breast cancer patients? - The EBCC 12 manifesto. *Breast* 2021; **55**: 128-35.

65. Brunt AM, Haviland JS, Kirby AM, et al. Five-fraction Radiotherapy for Breast Cancer: FAST-Forward to Implementation. *Clin Oncol (R Coll Radiol)* 2021.

66. Marta GN, Ramiah D, Kaidar-Person O, et al. The Financial Impact on Reimbursement of Moderately Hypofractionated Postoperative Radiation Therapy for Breast Cancer: An International Consortium Report. *Clin Oncol (R Coll Radiol)* 2021; **33**(5): 322-30.

67. Atun R, Jaffray DA, Barton MB, et al. Expanding global access to radiotherapy. *Lancet Oncol* 2015; **16**(10): 1153-86.

68. Laucis AM, Jagsi R, Griffith KA, et al. The Role of Facility Variation on Racial Disparities in Use of Hypofractionated Whole Breast Radiation Therapy. *Int J Radiat Oncol Biol Phys* 2020; **107**(5): 949-58.