



The Italian Association for Radiotherapy and Clinical Oncology (AIRO) position statements for postoperative breast cancer radiation therapy volume, dose, and fractionation

Icro Meattini^{1,2} · Isabella Palumbo³ · Carlotta Becherini² · Simona Borghesi⁴ · Francesca Cucciarelli⁵ · Samantha Dicuonzo⁶ · Alba Fiorentino⁷ · Ruggero Spoto⁸ · Philip Poortmans^{9,10} · Cynthia Aristei³ · Lorenzo Livi^{1,2}

Received: 18 August 2022 / Accepted: 19 September 2022 / Published online: 6 October 2022
© The Author(s) 2022

Abstract

Recent advances in non-metastatic breast cancer radiation therapy significantly reshaped our views on modern dose and fractionation schedules. Especially the advent of hypofractionation and partial breast irradiation defined a new concept of treatment optimization, that should strongly include both patient and tumour characteristics in the physician's decision-making process. Unfortunately, hypofractionation for breast cancer radiation therapy needed long time to enter the routine practice during the last decades despite the level-1 evidence published over time. Hereby we present the Italian Association for Radiotherapy and Clinical Oncology (AIRO) Breast Cancer Group position statements for postoperative breast cancer radiation therapy volume, dose, and fractionation to harmonically boost routine clinical practice implementation following evidence-based data.

Keywords Breast cancer · Radiotherapy · Hypofractionation · Guidelines · Ultra-hypofractionation · Partial breast irradiation

Introduction

Recent advances in non-metastatic breast cancer radiation therapy significantly reshaped our views on modern dose and fractionations schedules. Especially the advent of hypofractionation and partial breast irradiation defined a new concept of treatment optimization, that should strongly consider both patient and tumour features in the decision-making process. In this framework, the European Society for Radiotherapy and Oncology Advisory Committee in Radiation Oncology

Practice (ESTRO-ACROP) consensus recommendations on patient selection and dose and fractionation for external-beam radiotherapy in early breast cancer have been recently released [1].

To facilitate and enhance the breast oncologist's community harmony, the Italian Association for Radiotherapy and Clinical Oncology (AIRO) Breast Cancer Group felt the need for a prompt reaction to integrate this level-1 evidence in the routine clinical practice. Hereby we present the

✉ Icro Meattini
icro.meattini@unifi.it

¹ Department of Experimental and Clinical Biomedical Sciences “M. Serio”, University of Florence, Viale Morgagni 50, 50134 Florence, Italy

² Radiation Oncology Unit, Oncology Department, Azienda Ospedaliero Universitaria Careggi, Viale Morgagni 50, 50134 Florence, Italy

³ Radiation Oncology Section, University of Perugia and Perugia General Hospital, Perugia, Italy

⁴ Radiation Oncology Unit of Arezzo–Valdarno, Azienda USL Toscana Sud Est, Arezzo, Italy

⁵ Radiotherapy Unit, Azienda Ospedaliero Universitaria Ospedali Riuniti, Ancona, Italy

⁶ Division of Radiation Oncology, IEO, European Institute of Oncology, IRCSS, Milan, Italy

⁷ Radiation Oncology Department, General Regional Hospital F.Miulli, Acquaviva delle Fonti, Bari, Italy

⁸ Department of Radiotherapy, Humanitas Clinical and Research Center, IRCSS, Rozzano, Milan, Italy

⁹ Department of Radiation Oncology, Iridium Network, Antwerp, Belgium

¹⁰ Faculty of Medicine and Health Sciences, University of Antwerp, Antwerp, Belgium

position statements for postoperative breast cancer radiation therapy volume, dose, and fractionation.

Position statements

- a. *Hypofractionation is considered standard of care for all indication of external-beam postoperative breast cancer radiation therapy, regardless of the number and size of target volumes and breast reconstruction.* Hypofractionation is standard of care both for invasive and ductal carcinoma in situ of the breast. There is no reason to prescribe irradiation schedules using more than 15–16 fractions [1–6].
- b. *50 Gy in 25 fractions is no longer considered being standard of care.* It should be restricted to highly selected cases, such as concomitant chemoradiation and hyperthermia to enhance the radio-sensitisation effects of the combined systemic or local agents [3, 4].
- c. *5-fraction whole breast and/or chest wall irradiation without reconstruction (26 Gy in 5 fractions) is considered standard of care.* This schedule it is not to be considered experimental and should be considered the preferred option especially (but not exclusively) in patients fulfilling the inclusion criteria of the FAST-Forward trial [1, 7–9].
- d. *Moderate hypofractionation should be offered for regional nodal irradiation [1, 3, 4, 6].* Postmastectomy hypofractionated radiation therapy is non-inferior to and had similar toxicities to conventional fractionated radiation therapy in patients with high-risk breast cancer [6].
- e. *Partial breast irradiation is standard of care in selected patients affected by early breast cancer.* Especially (but not exclusively) in case of suitable features presence accordingly to the ESTRO-ACROP 2022 Consensus statements, partial breast irradiation should be preferred over whole breast irradiation [1, 10–18].

Discussion

The AIRO felt the strong needs for sake of clarity to endorse the recently published Consensus statements released in 2022 by the ESTRO-ACROP initiative [1]. Hypofractionation for breast cancer radiation therapy needed too much time to enter the routine clinical practice during the last decades despite the level-1 evidence published over time [1–6].

Hypofractionation for breast cancer radiation therapy passed through a long-lasting debate about its safety and efficacy, although there are no economic [19], radiobiologic [20], nor clinic reasons [2, 5, 21] to justify these uncertainties. And this fact was probably caused by several heterogeneous factors, such as shortage of experience in hypofractionation, minimal resources for quality assurance in radiotherapy, inadequate support to change, and reimbursement policies [1]. However, we strongly believe that one of the crucial boosts to harmonically implement evidence-based data in the routine practice of a Country is represented by a clear, transparent, and strong position statement released by the national Society of the leading discipline.

Endorsing the European ESTRO-ACROP initiative [1], in line with the UK Breast Radiotherapy Consensus Working Group [9], we would like to enhance and reinforce the evidence supporting hypofractionation for all the indications of external-beam postoperative radiation therapy for non-metastatic breast cancer, including whole and partial breast, chest wall with or without reconstruction, and regional nodal irradiation. If moderate hypofractionation (40–42.5 Gy in 15–16 fractions) represents the standard of care for all the above-mentioned indications, ultra-hypofractionation (26 Gy in 5 fractions) should be considered standard of care for whole breast irradiation and chest wall irradiation without reconstruction. Conversely, further data are awaited to confirm the recommendation in favour of ultra-hypofractionation concerning chest wall with reconstruction and regional nodal irradiation (Table 1).

Table 1 Volume, dose, fractionation AIRO breast cancer group recommendations

	50 Gy in 25 fractions	40–42.5 Gy in 15–16 fractions	26 Gy in 5 fractions
Whole breast irradiation	Not recommended	Recommended ^o	Recommended ^o
Partial breast irradiation	Not recommended	Recommended ^o	Recommended ^{o*}
Chest wall irradiation without reconstruction	Not recommended [^]	Recommended ^o	Recommended
Chest wall irradiation with reconstruction	Not recommended [^]	Recommended ^o	Not recommended
Regional nodal irradiation	Not recommended [^]	Recommended ^o	Not recommended

[^] Except for highly selected cases, such as concomitant chemoradiation and hyperthermia to enhance the radio-sensitisation effects of the combined systemic or local agents

^o Gold standard schedule

^{*} Gold standard for partial breast irradiation (26–30 Gy in 5, once-daily, consecutive fractions)

Table 2 Partial breast irradiation suitable patient selection criteria

Factor	Selection criteria
Patient-related	Age 50 years or more
Tumour-related	Luminal-like subtypes small tumour (≤ 3 cm) Clear surgical margins (> 2 mm) Node negative (including isolated tumour cells) Absence of lymph vascular space invasion Non-lobular invasive carcinoma Tumour grade 1–2 Low-to-intermediate grade DCIS, sized ≤ 2.5 cm, clear surgical margins (≥ 3 mm) Unicentric or unifocal
Treatment-related	No use of primary systemic therapy and neoadjuvant chemotherapy
<i>DCIS</i> ductal carcinoma in situ	

External-beam partial breast irradiation should be preferred over whole breast irradiation in case of clearly identified suitable features (Table 2) [1]. In these selected patients, partial breast irradiation using once-daily, consecutive fractions, schedule (40 Gy in 15 fractions or 26–30 Gy in 5 fractions) warrants equivalent disease control and a favourable safety toxicity profile [11, 14–17].

Fast implementation of short course radiation therapy schedules will warrant equity of access for all our patients. At the same time, benefits and risks, including uncertainties, of all available cancer treatments should be always discussed and shared with our patients, warranting an adequate counselling on the best evidence-based radiation therapy.

Acknowledgments The Authors thank the Scientific Committee and Board of the AIRO for the critical revision and final approval of the manuscript (Nr. 23/2022).

Author Contributions All authors contributed to the study conception and design, material preparation, data collection and analysis. The first draft of the manuscript was written by Icro Meattini, and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Funding Open access funding provided by Università degli Studi di Firenze within the CRUI-CARE Agreement. The authors declare that no funds, grants, or other support were received during the preparation of this manuscript.

Declarations

Conflict of interest IM received a small fee for occasional attendance at the advisory board supported by Eli Lilly, Novartis, Pfizer, Seagen, Accuray. PP is a medical adviser of Sordina IORT Technologies. All other authors declare no competing interests.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

Open Access This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third party material in this article are included in the article's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit <http://creativecommons.org/licenses/by/4.0/>.

References

- Meattini I, Becherini C, Boersma L, Kaidar-Person O, Marta GN, Montero A, Offersen BV, Aznar MC, Belka C, Brunt AM, Diuonzo S, Franco P, Krause M, MacKenzie M, Marinko T, Marrazzo L, Ratosi I, Scholten A, Senkus E, Stobart H, Poortmans P, Coles CE (2022) 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. *Lancet Oncol* 23(1):e21–e31. [https://doi.org/10.1016/S1470-2045\(21\)00539-8](https://doi.org/10.1016/S1470-2045(21)00539-8)
- Haviland JS, Owen JR, Dewar JA, Agrawal RK, Barrett J, Barrett-Lee PJ, Dobbs HJ, Hopwood P, Lawton PA, Magee BJ, Mills J, Simmons S, Sydenham MA, Venables K, Bliss JM, Yarnold JR (2013) 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* 14(11):1086–1094. [https://doi.org/10.1016/S1470-2045\(13\)70386-3](https://doi.org/10.1016/S1470-2045(13)70386-3)
- Marta GN, Coles C, Kaidar-Person O, Meattini I, Hijal T, Zissadis Y, Pignol JP, Ramiah D, Ho AY, Cheng SH, Sancho G, Offersen BV, Poortmans P (2020) The use of moderately hypofractionated post-operative radiation therapy for breast cancer in clinical

- practice: a critical review. *Crit Rev Oncol Hematol* 156:103090. <https://doi.org/10.1016/j.critrevonc.2020.103090>
4. Marta GN, Ramiah D, Kaidar-Person O, Kirby A, Coles C, Jaggi R, Hijal T, Sancho G, Zissiadis Y, Pignol JP, Ho AY, Cheng SH, Offersen BV, Meattini I, Poortmans P (2020) The financial impact on reimbursement of moderately hypofractionated postoperative radiation therapy for breast cancer: an international consortium report. *Clin Oncol (R Coll Radiol)*. <https://doi.org/10.1016/j.clon.2020.12.008>
 5. Whelan TJ, Pignol JP, Levine MN, Julian JA, MacKenzie R, Parpia S, Shelley W, Grimard L, Bowen J, Lukka H, Perera F, Fyles A, Schneider K, Gulavita S, Freeman C (2010) Long-term results of hypofractionated radiation therapy for breast cancer. *N Engl J Med* 362(6):513–520. <https://doi.org/10.1056/NEJMoA0906260>
 6. Wang SL, Fang H, Song YW, Wang WH, Hu C, Liu YP, Jin J, Liu XF, Yu ZH, Ren H, Li N, Lu NN, Tang Y, Tang Y, Qi SN, Sun GY, Peng R, Li S, Chen B, Yang Y, Li YX (2019) Hypofractionated versus conventional fractionated postmastectomy radiotherapy for patients with high-risk breast cancer: a randomised, non-inferiority, open-label, phase 3 trial. *Lancet Oncol* 20(3):352–360. [https://doi.org/10.1016/S1470-2045\(18\)30813-1](https://doi.org/10.1016/S1470-2045(18)30813-1)
 7. Coles CE, Aristei C, Bliss J, Boersma L, Brunt AM, Chatterjee S, Hanna G, Jaggi R, Kaidar Person O, Kirby A, Mjaaland I, Meattini I, Luis AM, Marta GN, Offersen B, Poortmans P, Rivera S (2020) International guidelines on radiation therapy for breast cancer during the COVID-19 pandemic. *Clin Oncol (R Coll Radiol)* 32(5):279–281. <https://doi.org/10.1016/j.clon.2020.03.006>
 8. Brunt AM, Haviland JS, Wheatley DA, Sydenham MA, Alhasso A, Bloomfield DJ, Chan C, Churn M, Cleator S, Coles CE, Goodman A, Harnett A, Hopwood P, Kirby AM, Kirwan CC, Morris C, Nabi Z, Sawyer E, Somaiah N, Stones L, Syndikus I, Bliss JM, Yarnold JR (2020) 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* 395(10237):1613–1626. [https://doi.org/10.1016/S0140-6736\(20\)30932-6](https://doi.org/10.1016/S0140-6736(20)30932-6)
 9. Lewis P, Brunt AM, Coles C, Griffin S, Locke I, Roques T (2021) Moving forward fast with FAST-forward. *Clin Oncol (R Coll Radiol)* 33(7):427–429. <https://doi.org/10.1016/j.clon.2021.04.007>
 10. Correa C, Harris EE, Leonardi MC, Smith BD, Taghian AG, Thompson AM, White J, Harris JR (2017) Accelerated partial breast irradiation: executive summary for the update of an ASTRO evidence-based consensus statement. *Pract Radiat Oncol* 7(2):73–79. <https://doi.org/10.1016/j.prro.2016.09.007>
 11. Meattini I, Marrazzo L, Saieva C, Desideri I, Scotti V, Simontacchi G, Bonomo P, Greto D, Mangoni M, Scoccianti S, Lucidi S, Paoletti L, Fambrini M, Bernini M, Sanchez L, Orzalesi L, Nori J, Bianchi S, Pallotta S, Livi L (2020) 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*. <https://doi.org/10.1200/JCO.20.00650>
 12. Meattini I, Saieva C, Miccinesi G, Desideri I, Francolini G, Scotti V, Marrazzo L, Pallotta S, Meacci F, Muntoni C, Bendinelli B, Sanchez LJ, Bernini M, Orzalesi L, Nori J, Bianchi S, Livi L (2017) Accelerated partial breast irradiation using intensity modulated radiotherapy versus whole breast irradiation: health-related quality of life final analysis from the florence phase 3 trial. *Eur J Cancer* 76:17–26. <https://doi.org/10.1016/j.ejca.2017.01.023>
 13. Polgar C, Van Limbergen E, Potter R, Kovacs G, Polo A, Lyczek J, Hildebrandt G, Niehoff P, Guinot JL, Guedea F, Johansson B, Ott OJ, Major T, Strnad V (2010) Patient selection for accelerated partial-breast irradiation (APBI) after breast-conserving surgery: recommendations of the Groupe European de Curiotherapie-European Society for Therapeutic Radiology and Oncology (GEC-ESTRO) breast cancer working group based on clinical evidence (2009). *Radiother Oncol* 94(3):264–273. <https://doi.org/10.1016/j.radonc.2010.01.014>
 14. Strnad V, Ott OJ, Hildebrandt G, Kauer-Dorner D, Knauerhase H, Major T, Lyczek J, Guinot JL, Dunst J, Miguez CG, Slampa P, Allgauer M, Lossl K, Polat B, Kovacs G, Fishedick AR, Wendt TG, Fietkau R, Hindemith M, Resch A, Kulik A, Arribas L, Niehoff P, Guedea F, Schlamann A, Potter R, Gall C, Malzer M, Uter W, Polgar C (2016) 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* 387(10015):229–238. [https://doi.org/10.1016/S0140-6736\(15\)00471-7](https://doi.org/10.1016/S0140-6736(15)00471-7)
 15. Vicini FA, Cecchini RS, White JR, Arthur DW, Julian TB, Rabinovitch RA, Kuske RR, Ganz PA, Parda DS, Scheier MF, Winter KA, Paik S, Kuerer HM, Vallow LA, Pierce LJ, Mamounas EP, McCormick B, Costantino JP, Bear HD, Germain I, Gustafson G, Grossheim L, Petersen IA, Hudes RS, Curran WJ Jr, Bryant JL, Wolmark N (2019) 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* 394(10215):2155–2164. [https://doi.org/10.1016/S0140-6736\(19\)32514-0](https://doi.org/10.1016/S0140-6736(19)32514-0)
 16. Whelan TJ, Julian JA, Berrang TS, Kim DH, Germain I, Nichol AM, Akra M, Lavertu S, Germain F, Fyles A, Trotter T, Perera FE, Balkwill S, Chafe S, McGowan T, Muanza T, Beckham WA, Chua BH, Gu CS, Levine MN, Olivetto IA, Investigators RT, Investigators RT (2019) 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* 394(10215):2165–2172. [https://doi.org/10.1016/S0140-6736\(19\)32515-2](https://doi.org/10.1016/S0140-6736(19)32515-2)
 17. Coles CE, Griffin CL, Kirby AM, Titley J, Agrawal RK, Alhasso A, Bhattacharya IS, Brunt AM, Ciurlionis L, Chan C, Donovan EM, Emson MA, Harnett AN, Haviland JS, Hopwood P, Jefford ML, Kaggwa R, Sawyer EJ, Syndikus I, Tsang YM, Wheatley DA, Wilcox M, Yarnold JR, Bliss JM, Trialists I (2017) 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* 390(10099):1048–1060. [https://doi.org/10.1016/S0140-6736\(17\)31145-5](https://doi.org/10.1016/S0140-6736(17)31145-5)
 18. Bhattacharya IS, Haviland JS, Kirby AM, Kirwan CC, Hopwood P, Yarnold JR, Bliss JM, Coles CE, Trialists I (2019) 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* 37(4):305–317. <https://doi.org/10.1200/JCO.18.00982>
 19. Lievens Y (2010) Hypofractionated breast radiotherapy: financial and economic consequences. *Breast* 19(3):192–197. <https://doi.org/10.1016/j.breast.2010.03.003>
 20. Haviland JS, Bentzen SM, Bliss JM, Yarnold JR, Group STM (2016) Prolongation of overall treatment time as a cause of treatment failure in early breast cancer: an analysis of the UK START (standardisation of breast radiotherapy) trials of radiotherapy fractionation. *Radiother Oncol* 121(3):420–423. <https://doi.org/10.1016/j.radonc.2016.08.027>
 21. Group ST, Bentzen SM, Agrawal RK, Aird EG, Barrett JM, Barrett-Lee PJ, Bentzen SM, Bliss JM, Brown J, Dewar JA, Dobbs HJ, Haviland JS, Hoskin PJ, Hopwood P, Lawton PA, Magee BJ, Mills J, Morgan DA, Owen JR, Simmons S, Sumo G, Sydenham MA, Venables K, Yarnold JR (2008) The UK standardisation of breast

radiotherapy (START) trial B of radiotherapy hypofractionation for treatment of early breast cancer: a randomised trial. *Lancet* 371(9618):1098–1107. [https://doi.org/10.1016/S0140-6736\(08\)60348-7](https://doi.org/10.1016/S0140-6736(08)60348-7)

Publisher's Note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.