Adjuvant hypofractionated radiotherapy with simultaneous integrated boost after breast-conserving surgery: A systematic literature review

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\section*{A R T I C L E   I N F O}

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\section*{A B S T R A C T}

\textbf{Aims:} Several studies have shown that simultaneous integrated boost provides better dose homogeneity, improves the biologically effective dose-volume histogram and reduces treatment time compared to sequential boost in breast cancer.

\textbf{Patients and methods:} We conducted a systematic review of published trials evaluating simultaneous integrated boost in hypofractionated radiotherapy to analyze the results in terms of overall survival, local control, early and late side effects, and radiotherapy techniques used.

\textbf{Results:} Upon 9 articles, the prescribed dose to the whole breast varied from 40 to 46.8 Gy. The number of fractions varies from 15 to 20 fractions. The prescribed dose per fraction to the boost varied from 2.4 Gy per fraction to 3.4 Gy per fraction for a total boost dose from 48 to 52.8 Gy.

\textbf{Conclusions:} Simultaneous integrated boost seems effective and safe when given hypofractionated whole-breast irradiation but needs to be validated in prospective trials.

\section*{Introduction}

Breast cancer is the most common cancer in women worldwide, as it is also the leading cause of cancer death among women globally [1]. The use of radiotherapy in the adjuvant setting has improved both local control and overall survival in early-stage breast cancer patients [2].

Moderate hypofractionation is the standard of care for breast cancer requiring adjuvant radiotherapy. Several randomized controlled trials showed the equivalence of hypofractionated radiotherapy for local tumor control and the rates of late adverse effects in early breast cancer. In these trials, the boost to the tumor bed was performed sequentially with breast irradiation, thus prolonging the duration of treatment [3–5].

Simultaneous integrated boost (SIB) was introduced in combination with conventionally fractionated whole-breast irradiation (WBI) with advanced imaging techniques for accurate pretreatment staging and positioning and availability of daily image guidance before every radiotherapy session. Several studies have shown that SIB provides better dose homogeneity, improves the biologically effective dose-volume histogram and reduces treatment time compared to sequential boost [6–8]. Performing SIB with hypofractionated whole-breast irradiation would further reduce the overall treatment time.

In light of the literature, we conducted a systematic review of published trials evaluating SIB in hypofractionated radiotherapy for breast cancer to analyze the results in terms of overall survival (OS), local control, early and late side effects, and radiotherapy techniques used.

\section*{Materials and methods}

For our article research, we followed the PRISMA guidelines [9]. A research protocol was published in the PROSPERO database (registration number: 297495). Articles corresponding to the Mesh terms “breast cancer” and “adjuvant radiotherapy” and the terms “hypofractionated” and “simultaneous integrated boost” were searched in the PubMed database. Articles corresponding to the terms “breast cancer”, “adjuvant radiotherapy”, “hypofractionated” and “simultaneous integrated boost” were searched in the Cochrane library. Studies published since 2015 reporting prospective trials published in English or French were
included. We closed the search on 31 December 2021. The flow diagram for our methods is shown in Fig. 1. Twenty-three articles were retrieved using PubMed. One article was retrieved through the references of another article. Fourteen articles were excluded because they did not meet the inclusion criteria. In each article, we collected the following data: the number of patients, the median age of patients, median follow-up, radiotherapy modalities, number of fractions, dose delivered to the breast, dose delivered to the boost, clinical outcomes and dosimetric outcomes.

Results

A total of 9 articles were reviewed. The characteristics of the studies are reported in Table 1. The articles were published from 2012 to 2021 [10–18]. Two trials were randomized and controlled [17,18]. One trial was multicentric [11]. The median follow-up ranged from 12 months to 86.4 months, with two trials without reported follow-up values.

Patient population

Patient and tumor characteristics are reported in Table 2. The number of patients ranged from 10 [15] to 151 [11]. The median age ranged from 47.9 years [15] to 68 years [16], and one trial did not report the median age of the included patients [12].

Tumor characteristics

All articles except two articles [14,17] reported study tumor characteristics. Concerning the pTNM stage, the authors mainly included patients with pT1 tumors, except for the series by Mondal et al. that included 80% of patients with pT2 tumors [15]. The proportion of pN1 varied, according to the articles, from 5% [13] to 40% [15]. The majority of patients had tumors expressing hormone receptors but not expressing HER2 receptors (Table 2). Only three articles reported the volume of the boost [10,15–17]. Mondal et al. reported a mean volume of PTV boost of 228.9 cc [15]. Van Hulle et al. reported respectively a mean volume of boost in SEB arm and SIB arm of 41.86 cc (SD 27.87) and 37.81 cc (SD 31.37) [17]. Scorsetti et al. reported a mean volume of PTV boost of 51.5 cc (±45.9) [16]. De Rose et al. reported the mean dose delivered at PTV boost according to the presence or absence of liponecrosis in patients, respectively, of 48 cc (±8) and 37 cc (±4) [10].

Irradiation technique

All studies except one [17] reported the irradiation technique. The irradiation techniques used were tridimensional radiotherapy (3DRT) [14], 3DRT or intensity-modulated radiotherapy (IMRT) in 59 and 41% for Krug et al. [13] and 30 and 70% for Dellas et al. [11], volumetric modulated arc therapy (VMAT) [10,15,16], tomotherapy [18] and tomotherapy with statics ports (TomoDirect) [12]. The authors of the three articles did not report the energy of the prescribed irradiation beams [12,17,18]. All the others treated their patients with 6 MV beams (Table 1).

Radiation therapy prescription

The prescribed dose to the whole breast varied from 40 to 46.8 Gy, with fraction numbers varying from 15 to 20 fractions. The total
prescribed dose to the boost varied from 48 to 52.8 Gy. The prescribed dose per fraction to the boost varied from 2.4 Gy per fraction to 3.4 Gy per fraction for a total boost dose from 48 to 52.8 Gy (Table 1).

Dosimetric outcomes

Dosimetric and clinical outcomes are reported in Tables 3 and 4. Four articles reported dosimetric outcomes [12,13,15,16]. The mean $D_{98\%}$ (maximal dose covering 2% of the planned target volume) and $D_{2\%}$ (dose covering 98% of the planned target volume) varied to breast PTV from 105.1% to 118.5% and 91.8% to 95.1%, respectively. The mean $D_{98\%}$ and $D_{2\%}$ varied to boost the PTV from 101.8% to 107.4% and 95.1% to 96.2%, respectively [12,15,16].

Clinical outcomes

The majority of patients did not develop any acute skin reactions or grade 1 skin reactions to the radiotherapy. Acute skin reactions of grade 3 ranged from 0 to 2%. One trial did not report acute skin toxicity [18].

Four articles did not report an analysis of late skin toxicity [11,13,15,18]. De Rose et al. reported a one-year grade 1 dermatitis rate of 14% [10]. Van Hulle et al. compared sequentially and simultaneously integrated boost arms and reported rates of breast retraction 25.6% and 22.1% (p = 0.5), edema 7.3% and 4.3% (p = 0.5), telangiectasia 7.3% and 5.8% (p = 0.9), fibrosis outside the tumor bed 12.7% and 13% (p = 0.9), fibrosis in the tumor bed 9.1% vs. 7.2% (p = 0.7) and pigmentation 17.6% and 22.1% (p = 0.6), respectively [17].

Regarding local control, 5 studies reported the number of local recurrences. No one reported local recurrence in patients treated with SIB [10,12,15-17]. The median follow-up was 12 months for two of these studies [12,16] and 24 months for the other three [10,15,17]. Van Hulle et al. reported one local recurrence in a group of 74 patients treated with sequential boost [17].

Discussion

The role of the boost to the surgical bed remains an object of debate, especially in the case of hypofractionated whole-breast irradiation. In the Canadian trial led by Whelan et al., patients did not receive any boosts. Still, the risk of local relapse at 10 years was only 7.5%, suggesting that the influence of the boost to the surgical bed could be limited [4]. In START A and B trials, 63% and 41% of patients received a boost, respectively [3,5]. None of the trials in this systematic review of the literature reported survival data. Recently, French national guidelines (RECORAD 2021) maintained the boost in patients under 50 years of age and did not provide conclusions regarding the benefit of SIB [19]. The European Society for Radiotherapy and Oncology (ESTRO) has unanimously retained the boost in the case of HF-WBI [20].

Concerning SIB in the case of HF-WBI, there are two large phase III prospective trials comparing sequential boost vs. SIB. The RTOG 1005 trial (NCT01349322) is a phase III prospective trial comparing conventional radiotherapy (50 Gy in 25 fractions or with hypofractionation option of 42.7 Gy in 16 fractions) followed by a sequential boost of 12–14 Gy in 6–7 fractions vs. a hypofractionated WBI schedule of 40.05 Gy in 15 fractions with an SIB to the tumor bed up to 48 Gy. No lymph node irradiation is planned in this trial [21]. The IMPORT HIGH trial (NCT00818051) assessed dose-escalated RT delivered with IMRT in early breast cancer patients. The standard arm comprises 40.5 Gy in 15 fractions and a sequential tumor bed boost of 16 Gy in 8 fractions. The two experimental arms are described as follows: patients in the first arm received 15 fractions of 2.4 Gy, 2.67 Gy and 3.2 Gy to the whole breast, the index quadrant and the tumor bed, respectively, while patients in the second arm received 15 fractions of 3.53 Gy to the tumor bed. The irradiation or absence of irradiation of lymph nodes is not specified in the trial protocol [22]. The 5-year results of IMPORT HIGH were presented in an abstract at ESTRO 2021. The estimated 5-year ipsilateral

Table 1

| Authors | Publication date | Randomization | Controlled trial | Primary objective | Follow-up time (months) | Number of patients | Number of fractions | Whole breast dose per fraction (Gy) | Boost dose per fraction (Gy) | Technique | Dose per fraction (Gy) | Energy (MV) | Technique |
|---------|-----------------|---------------|-----------------|-------------------|------------------------|--------------------|-------------------|-------------------------------|--------------------------|-----------|-------------------|------------|-----------|
| Versmessen et al. [18] | 2012 | 1 | 1 | Quality of life | 121 | 55 | 15 | 2.8 | 3.4 | Tomotherapy | NA | 6 |
| Scorsetti et al. [16] | 2012 | 0 | 0 | Feasibility | 50 | 12 | 68 | 15 | 2.7 | 3.2 | VMAT | 6 |
| Dellas et al. [11] | 2014 | 0 | 0 | Feasibility | 151 | NA | 61 | 16 | 2.5 | 3.0 | 3DRT or IMRT | 6 |
| De Rose et al. [10] | 2016 | 0 | 0 | Cosmetic | 144 | 24 | 62 | 15 | 2.7 | 3.2 | VMAT | 6 |
| Mondal et al. [15] | 2017 | 0 | 0 | Feasibility | 10 | 24 | 67 | 20 | 2.25 | 2.5 | Tomodirect | NA |
| Lertbutsayanukul et al. [14] | 2020 | 0 | 0 | Patient-rated toxicity | 114 | 86.4 | 50.8 | 16 | 2.7 | 3.3 | 3DRT | 6 |
| De Rose et al. [10] | 2016 | 0 | 0 | Cosmetic | 149 | NA | 61 | 15 | 2.5 | 3.0 | 3DRT and IMRT | 6 |

3DRT: three-dimensional radiotherapy, Gy, gray; IMRT, intensity-modulated radiation therapy, NA, not available; VMAT, volumetric-modulated arc therapy.
### Table 2
Patient and tumor characteristics.

| Authors                | pT1a (%) | pT1b (%) | pT1c (%) | pT2 (%) | pN0 (%) | pN1 (%) | grade SBR 1 (%) | grade SBR 2 (%) | grade SBR 3 (%) | HR status + (%) | HR status - (%) | HER2 + (%) | HER2 - (%) |
|------------------------|----------|----------|----------|---------|---------|---------|----------------|----------------|----------------|----------------|----------------|------------|------------|
| Versmessen et al. [18] | 63.6     | 36.3     | 77.4     | 30.6    | 27.2    | 44.6    | 23             | 84.2           | 15.8           | 10.7           | 89.3           | NA         | NA         |
| Scorsetti et al. [16]  | 11       | 21       | 38       | 28      | 92      | 8       | 19             | 72             | 9              | 92             | 8              | 2          | 98         |
| Franco et al. [12]     | 8        | 26       | 48       | 12      | 71      | 23      | 21             | 55             | 24             | 92             | 8              | 17         | 83         |
| Dellas et al. [11]     | 5        | 24.8     | 47.5     | 19.2    | 92.2    | 7.8     | NA             | NA             | NA             | NA             | 57.4          | 9.9        | 19.4       |
| De Rose et al. [10]    | 2.8      | 25       | 53.5     | 16      | 84.7    | 11.8    | 11.1           | 70.8           | 15.3           | 94.3           | 4.2           | 4.2        | 13.2       |
| Mondal et al. [15]     | 0        | 0        | 20       | 80      | 60      | 40      | 0              | 80             | 70             | 30             | 20            | 80         | 80         |
| Lertbutsayanukul et al. [14] | NA      | NA      | NA       | NA      | NA      | NA      | NA             | NA             | NA             | NA             | NA            | NA         | NA         |

HER 2: Human epidermal growth factor receptor-2; HR: hormonal receptor; NA: not available; SBR: Scarff Bloom Richardson.

### Table 3
Dosimetric and clinical outcomes.

| Authors                | Conformity index | Homogeneity index | Dosimetry | Cardiac side effect | Pulmonary side effect | Acute skin toxicity | Late skin toxicity | Cosmetic results | Ipsilateral breast tumor relapse |
|------------------------|------------------|-------------------|-----------|---------------------|-----------------------|---------------------|---------------------|-------------------|-------------------------------|
| Versmessen et al. [18] | NA               | NA                | –         | NA                  | NA                    | grade 0: 40% grade 1: 64% grade 2: 0% grade 3: 2% grade 4: 0% | NA                  | comparable between treatment arms | excellent/good: 100% | NA               |
| Scorsetti et al. [16]  | NA               | NA                | PTVWB:    | NA                  | NA                    | grade 0: 41% grade 1: 53% grade 2: 6% grade 3: 1% | grade 1: 5% grade 2: 2% grade 3: 4: 0% | grade 1: 1% grade 2: 6% grade 3: 0% | grade 4: 0% | excellent: 69% | good: 22% | fair: 5% | 0 |
| Franco et al. [12]     | NA               | NA                | PTVWB:    | NA                  | NA                    | grade 0: 49.7% grade 1: 41.8% grade 2: 8.5% grade 3: 0% | grade 0: 8% grade 3: 0% grade 4: 0% | grade 1: 14% grade 3: 4: 0% | grade 1: 1% grade 2: 6% grade 3: 0% | grade 4: 0% | grade 1: 1% grade 2: 6% grade 3: 0% | grade 4: 0% | 0 |
| Dellas et al. [11]     | NA               | NA                | PTVWB:    | NA                  | NA                    | grade 0: 80% grade 2: 20% grade 3: 4: 0% | grade 1: 100% | NA good-excellent: 100% | NA | 0 |
| De Rose et al. [10]    | NA               | NA                | PTVWB:    | NA                  | 0                    | Pulmonary fibrosis G1: 36 patients (25%) | grade 1: 1% grade 2: 6% grade 3: 0% grade 4: 0% | grade 1: 1% grade 2: 6% grade 3: 0% | grade 4: 0% | grade 1: 1% grade 2: 6% grade 3: 0% | grade 4: 0% | 0 |
| Mondal et al. [15]     | PTVWB: 0.97      | PTVBOOST: 0.97    | PTVWB: 1.2| PTVBOOST: 1.1       | NA                    | NA                  | grade 1: 2: 91.3% vs. 73.7% in C-SIB and H-SIB arms (p = 0.048) | grade 1: 1% grade 2: 6% grade 3: 0% grade 4: 0% | grade 1: 1% grade 2: 6% grade 3: 0% | grade 4: 0% | grade 1: 1% grade 2: 6% grade 3: 0% | grade 4: 0% | NA |
| Lertbutsayanukul et al. [14] | NA      | NA                | NA        | NA                  | NA                    | NA                  | grade ≤1: 122 pts grade 2: 3: 21 pts grade 4: 0 pts | NA | NA | NA | 1 pts in SEB arm |
| Krug et al. [13]       | NA               | NA                | NA        | NA                  | NA                    | grade 3: 4: 0% | NA | NA | NA | 1 pts in SEB arm |
| Van Hulle et al. [17]  | NA               | NA                | NA        | NA                  | NA                    | NA                  | NA | NA | NA | 1 pts in SEB arm |

C-SIB: conventional simultaneous integrated boost; D_{95%}: maximal dose covering 2% of the planning target volume; D_{98%}: dose covering 98% of the planning target volume; Gy: Gray; H-SIB: hypofractionated simultaneous integrated boost; PTVBOOST: planning target volume boost; PTVWB: planning target volume whole breast; SEB: sequential boost.
Table 4
Dosimetric outcomes at organs at risk.

| Authors                  | Heart                                      | Ipsilateral lung                                | Contralateral lung                               | Contralateral breast  |
|-------------------------|--------------------------------------------|-------------------------------------------------|-------------------------------------------------|-----------------------|
| Vernimmenes et al. [18] | Dmean = 5.4 Gy ± 2.0                      | Dmean = 8.7 Gy ± 1.7                            | Dmean = 2.5 Gy ± 0.9                             | Dmean = 3.3 Gy ± 5.8  |
|                         | D5cc = 20.4 Gy ± 8.9                      | V50 Gy = 61.9% ± 15.9                           | V50 Gy = 8.9% ± 9.9                             | V50 Gy = 7.6% ± 15.0  |
| Franco et al. [12]     | **                                      | Dmean = 2.1 Gy ± 1.2                            | Dmax = 2.1 Gy ± 1.1                             | Dmax = 2.9 Gy ± 1.3   |
|                         | Dmean = 25.1 Gy ± 19.1                    | V50 Gy = 9.6% ± 3.1                             | V50 Gy = 6.4 Gy ± 1.5                           |                       |
| Dellas et al. [11]     | Dmedian = 1.4 Gy [0.4–4.6]                | Dmax = 45 Gy [0.0–48.8]                         | Dmedian = 2.5 Gy ± 1.3                          | Dmedian = 0.1 Gy [0.0–41] |
| De Rose et al. [10]    | Dmean = 5.1 Gy ± 2.1                      | Dmean = 7.6 Gy ± 1.5                            | Dmean = 2.5 Gy ± 1.3                            | Dmean = 2.3 Gy ± 0.6  |
| Mondal et al. [15]     | Dmean = 6.22 Gy [4.17–8.4]               | Dmean = 13.92 Gy [7.39–21.61]                   | Dmean = 4.05 Gy [2.33–6.39]                     | Dmax = 35.51 Gy [23.9–45.12] |
|                         | V10 Gy = 0% ± 0.0                         | V20 Gy = 7.6% ± 2.7                             | V20 Gy = 50.9% ± 14.7                          | Dmax = 6.35 Gy [4.59–8.67] |
| Lertbutiyukanukul et al. [14] | Dmean = 4.24% ± 0.0          | V50 Gy = 21.5% [8.89–36.5]                      | V50 Gy = 0.62% [0.0–3.33]                       |                       |
| Krug et al. [13]       | NA                                         | V20 Gy = 47.7% [38.34–54.29]                    | V20 Gy = 12.66% [4.83–21.43]                    |                       |
| Van Hulle et al. [17]  | NA                                         | V50 Gy = 15.6% ± 3.4                            | NA                                               |                       |

*: only left sided tumor; D_{5cc}: maximal dose covering 1 cubic centimeter of the planning target volume; Dmax: maximal dose; Dmean: mean dose; Dmedian: median dose; Gy: Gray; V: Volume expressed as a percentage receiving x Gray.

Krug et al. reported a mean dose to the breast planning target volume (PTV) and boosted PTV of 40.01 ± 0.12 Gy and 48.01 ± 0.08 Gy, respectively [13]. Mondal et al. reported conformity indices for the breast PTV and the boost PTV was equal to 0.97. The homogeneity indices reported for the breast PTV and boost PTV were equal to 1.2 and 1.1, respectively [15].

breast recurrence incidence was 1.9% (95% CI 1.2–3.1) for 40 + 16 Gy, 2.0% (95% CI 1.2–3.2) for 48 Gy, and 3.2% (95% CI 2.2–4.7) for 53 Gy. Five-year AE data were available for 1894 clinician assessments. The 5-year moderate/marked side effects rates were broadly similar between the groups and the control, with a higher risk of clinically assessed breast induration, breast distortion, and patient-assessed breast hardness/firmness for 53 Gy versus 48 Gy. Both trials have been closed to accrual, and the results will provide evidence on this debated issue. While waiting for these results, it might be interesting to perform a meta-analysis on the subject for a quantitative and rigorous evaluation of these data.

Conclusion

The number of acute toxicities of grade ≥2 was low. The late cosmetic results are also encouraging, SIB with HF-WBI does not seem to increase late toxicities. Although follow-up was short, no local recurrence was described, except for one local recurrence in the sequential boost arm in a single trial. SIB was well tolerated when given with HF-WBI. The RTQG 1005 and IMPORT HIGH trials will probably confirm these results. However, trials considering lymph node irradiation with HF-WBI and SIB seem relevant.

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Declaration of Competing Interest

The authors have no conflicts of interest to declare.

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References

[1] H. Sung, J. Ferlay, R.L. Siegel, M. Laversanne, I. Soerjomataram, A. Jemal, et al., Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries, CA Cancer J. Clin. 71 (3) (2021) 209–49.

[2] Effect of radiotherapy after breast-conserving surgery on 10-year recurrence and 15-year breast cancer death: meta-analysis of individual patient data for 10 801 women in 17 randomised trials, Lancet 376 (9740) (2010) 1707–16, nov.

[3] S.T.A.R.T. Trialists' Group, S.M. Bentzen, R.K. Agrawal, E.G.A. Aird, J.M. Barrett, P.J. Barrett-Lee, et al., The UK Standardisation of Breast Radiotherapy (START) trial B of radiotherapy hypofractionation for treatment of early breast cancer: a randomised trial, Lancet 371 (9618) (2008) 1098–107, 29 mar.

[4] T.J. Whelan, J.P. Pignol, M.N. Levine, J.A. Julian, R. MacKenzie, S. Parpia, et al., **Inex Menoux:** Methodology, Validation, Writing – review & editing. **Carole Mathelin:** Validation, Writing – review & editing. **Georges Noël:** Conceptualization, Methodology, Supervision, Writing – review & editing.

[5] S.M. Bentzen, R.K. Agrawal, E.G.A. Aird, J.M. Barrett, P.J. Barrett, et al., START Trialists' Group, The UK Standardisation of Breast Radiotherapy (START) trial A of radiotherapy hypofractionation for treatment of early breast cancer: a randomised trial, Lancet Oncol. 9 (4) (2008) 331–41, 1 avr.
Translational Oncology 22 (2022) 101456

M.M.O.M. Aly, G. Glattling, L. Jahnke, F. Wenz, Y. Abo-Madyan, Comparison of breast simultaneous integrated boost (SIB) radiotherapy techniques, Radiat. Oncol. 10 (1) (2015) 139, 9 juill.

H. Van Parijs, G. Miedema, V. Vinh-Hung, S. Verbanck, N. Adriaensens, D. Kerkhove, et al., Short course radiotherapy with simultaneous integrated boost for stage I-II breast cancer, early toxicities of a randomized clinical trial, Radiat. Oncol. 7 (2012) 80, 1 juin.

H. Van Parijs, T. Reynders, K. Heuninckx, D. Verellen, G. Storme, M. De Ridder, Breast conserving treatment for breast cancer: dosimetric comparison of sequential versus simultaneous integrated photon boost, BioMed Res. Int. 2014 (2014), e827475, 4 août.

D. Moher, et al., Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement, PLoS Medicine (2009), https://doi.org/10.1371/journal.pmed.1000097.

F. De Rose, A. Fogliata, D. Franceschini, P. Navarria, E. Villa, C. Iftode, et al., Phase II trial of hypofractionated VMAT-based treatment for early stage breast cancer: 2-year toxicity and clinical results, Radiat. Oncol. 11 (1) (2016) 120, 17 sept.

K. Della, K. Vonthein, J. Zimmer, S. Dinges, A.D. Boicev, P. Andreas, et al., Hypofractionation with simultaneous integrated boost for early breast cancer: results of the German multicenter phase II trial (ARO-2010-01), Strahlenther. Onkol. 190 (7) (2014) 646–53, juill.

P. Franco, M. Zeverino, F. Migliaccio, D. Cante, P. Sciacero, V. Casanova Borca, et al., Intensity-modulated and hypofractionated simultaneous integrated boost adjuvant breast radiation employing statics ports of tomotherapy (TomoDirect): a prospective phase II trial, J. Cancer Res. Clin. Oncol. 140 (1) (2014) 167–77, janv.

D. Krug, R. Baumann, K. Krockenberger, R. Vonthein, A. Schreiber, A. Boicev, et al., Adjuvant hypofractionated radiotherapy with simultaneous integrated boost after breast-conserving surgery: results of a prospective trial, Strahlenther Onkol. 197 (1) (2021) 48–55.

C. Lertbutsayanarkul, M. Pitak, N. Achaiyasongkram, N. Rakkit, F. Seuree, A. Prayongrat, Long-term patient-rated cosmetic and satisfactory outcomes of early breast cancer treated with conventional versus hypofractionated breast irradiation with simultaneous integrated boost technique, Breast J. 26 (10) (2020) 1946–52, oct.

D. Mondal, P.K. Julka, D.N. Sharma, M. Jana, M.A. Laviraj, S.V. Deo, et al., Accelerated hypofractionated adjuvant whole breast radiation with simultaneous integrated boost using volumetric modulated arc therapy for early breast cancer: a phase I/II dosimetric and clinical feasibility study from a tertiary cancer care centre of India, J. Egypt. Natl. Cancer Inst. 29 (1) (2017) 39–45, mars.