Strahlenther Onkol 2013 · 189:193–196
DOI 10.1007/s00066-012-0300-3
Published online: 30. Januar 2013
© Springer-Verlag Berlin Heidelberg 2013

F. Sedlmayer¹ · M.L. Sautter-Bihl² · W. Budach³ · J. Dunst⁴ · P. Feyer⁵ · R. Fietkau⁶ · W. Haase⁷ · W. Harms⁸ · C. Rödel⁹ · R. Souchon¹⁰ · F. Wenz¹¹ · R. Sauer⁶
Breast Cancer Expert Panel of the German Society of Radiation Oncology (DEGRO)

¹ Department of Radiotherapy and Radiation Oncology, LKH Salzburg,

Paracelsus Medical University Hospital, Salzburg

² Klinik für Radioonkologie und Strahlentherapie, Städtisches Klinikum Karlsruhe

³ University Hospital Düsseldorf

⁴ University Hospital Schleswig-Holstein, Lübeck

⁵ Klinikum Neukoelln, Berlin

⁶ University Hospital Erlangen

⁷ formerly St.-Vincentius-Kliniken, Karlsruhe

⁸ St. Clara Hospital, Basel

⁹ University Hospital Frankfurt/Main

¹⁰ University Hospital Tübingen

¹¹ University Hospital Mannheim

Is the simultaneously integrated boost (SIB) technique for early breast cancer ready to be adopted for routine adjuvant radiotherapy?

Statement of the German and the Austrian Societies of Radiooncology (DEGRO/ÖGRO)

Adjuvant radiotherapy following breast conserving surgery (BCS) is usually performed by homogenous irradiation of the whole breast (WBI), using single doses of 1.8–2 Gy up to total doses around 50 Gy, mostly followed by a boost to the tumor bed considered as the area of highest subclinical tumor cell contamination [19]. This tumor bed boost may be applied using external photon and/or electron beams up to cumulative tumor bed doses of 60–66 Gy in same fractional dose sizes as the preceding WBI. Alternatively, higher single fractions around 10 Gy are commonly used for either brachytherapy or intraoperative tumor bed boosts (IORT).

During the last few years, a new method of dose escalation to the tumor bed by a simultaneously integrated boost (SIB, concomitant boost) was proposed [11]. The rationale is a localized dose enhancement in the area at highest risk without prolonging treatment duration, thus not only providing improved patient comfort

but also exploiting the higher sensitivity of breast tumor cells towards larger single doses, which has long been postulated in the linear-quadratic model. On the other hand, the same model also predicts increased responsiveness of all normal structures which are relevant for late reaction developments and hence, cosmetic outcome following radiotherapy during BCT (e.g. skin, subcutaneous tissue, ribs [9]).

This topic was addressed by Bantema-Joppe et al. [1] who recently reported their experience with the SIB technique in a publication that prompted the present editorial. Between 2005 and 2010, 940 patients were treated by standard-fractionated WBI (28 fractions of 1.8 Gy) and SIB regimen of 2.3–2.4 Gy. Toxicity and cosmetic results were evaluated annually. After a median follow-up period of 30 months (6–54 months) grade ≥ 2 fibrosis in the boosted area was observed in 8.5% of the patients, chest wall pain

in 6.7%, and grade ≥ 2 teleangiectasia in 3.7%. Half of all patients developed fibrosis outside the boost volume (all grades). In 39.7% of all cases, the cosmetic outcome was scored as acceptable or poor. In multivariate analysis, no RT-related parameter was identified as predictive for the increase of late reactions or inferior cosmetic results. Quantitative information on absolute boost volumes and outcome analyses along volume sizes were not provided. The authors interpreted their results as in accordance with findings after “classical” RT with consecutive boosts, although they admitted that the cumulative rates of observed fibrosis were in the upper range of reports. Nonetheless, their conclusion was that the technique was “safe regarding normal tissue complications”. In a former publication they had evaluated 3-year locoregional control, recurrence-free and overall survival (OS) rates of 99.2%, 95.5%, and 97.1% [2].

The role of fraction size for breast cancer radiotherapy

The Canadian and British hypofraction trials provided first experiences with reduced total whole breast doses in comparison to conventional 50 Gy WBI in 2 Gy fractions, testing the radiobiological hypothesis of iso-effectiveness in terms of tumor sterilization without increasing long-term toxicity [22, 24]. To date, clinical intermediate- and long-term analyses seem to confirm the above mentioned biomathematical models in terms of assumed α/β (α/β) values of all relevant tissues regarding both, tumor control and cosmetic results. Nevertheless, longer follow-up remains necessary to confirm these observations by more mature data.

Another open issue is whether the existing clinical data for hypofractionated WBI can safely be transferred to WBI using SIB strategies in general practice. Generally, SIB techniques can be performed within conventionally (normo-)fractionated WBI (single breast doses 1.8–2 Gy, total doses 50 Gy) as well as hypofractionated WBI schedules (single doses around 2.7 Gy, total dose around 40 Gy). Thus, SIB doses to the tumor bed amount to 2.4–2.6 Gy during conventional and 3.0–3.2 Gy during hypofractionated WBI, respectively.

During normofractionated WBI, SIB doses of 10–16 Gy are administered in 25–28 fractions, leading to areas of daily zonal dose augmentations of 20–35% of the prescribed whole-breast dose. In contrast to the above quoted hypofractionation trials, the total number of WBI fractions is however not reduced. Therefore, dependent on number and dosage of SIB fractions, the LQ model predicts somewhat higher rates of late reactions within the tumor bed volume (see below). Moreover, the role of dose inhomogeneities in these dimensions during WBI is not clarified. Especially in larger breast volumes, they have been associated with significantly higher rates of subsequent development of breast fibrosis with worse cosmetic outcome [12, 16]. Unlike in SIB treatments, these regional overdoses were inadvertent effects caused by patients' anatomy and lower depth penetration of photons (partly cobalt-60) in the absence

of in-field modulation options. Therefore, caution has to be exercised when a former shortcoming in dose homogeneity, which was systematically optimized by the evolvement of sophisticated EBRT techniques, is purposely re-introduced under the assumption of a biologic superiority.

The negative cosmetic impact of larger volumes exposed to higher doses has been described several times [7, 16, 21]. However, data elucidating the role of such dose-volume relations are too sparse to permit a reliable estimation of the normal breast tissue's cost-benefit risk during dose homogeneity modulations [17]. Moreover, opinions are dissenting on how to adopt the LQ model for prediction of late reactions. For instance, some studies on accelerated partial breast irradiation (APBI) show markedly higher rates of fibrosis and unacceptable cosmetic results following zonal single doses of 3.85 Gy in 10 fractions over 5 consecutive days—even without WBI [15]. This observation was interpreted by Bentzen and Yarnold [3] as a possible overestimation of cell repair capacities within the interval of a hypofractionated RT and/or as consequence of overvalued α/β ratios for the estimation of cosmetically relevant late effects. To date, the most frequently used α/β figures for chronic skin/subcutaneous tissue reactions range between 2.8 and 3.4 Gy.

To further elucidate the possible risks and consequences of a defined SIB schedule (especially when used outside clinical trials), some systematic—albeit hypothetical—calculations are convenient. For estimation of late fibrosis, an averaged α/β value of 3 Gy is used:

- after conventional WBI (25 fractions of 2 Gy) followed by a tumor bed boost of 10 Gy (5 fractions of 2 Gy), the 2 Gy per fraction equivalent dose (2 Gy ED) in the boost area is 60 Gy, and after a booster dose of 16 Gy (8 fractions of 2 Gy), the BED amounts to 66 Gy, respectively. Correspondingly, single doses of 1.8 Gy for WBI and boost up to a total tumor bed dose of 66.6 Gy result in a 2 Gy ED of 63.9 Gy;
- SIB treatments with single doses of 2.1 Gy during conventional WBI (28 fractions of 1.8 Gy WBI, 28 fractions of 2.1 Gy SIB) result in 2 Gy ED of 60 Gy;

- SIB treatments with single doses of 2.25 Gy during conventional WBI (28 fractions of 1.8 Gy WBI, 28 fractions of 2.25 Gy SIB) result in 2 Gy ED of 66.2 Gy;
- SIB treatments with single doses of 2.25 Gy during conventional WBI (25 fractions of 2.0 Gy WBI, 25 fractions of 2.25 Gy SIB) result in 2 Gy ED of 59.1 Gy;
- SIB treatments with single doses of 2.4 Gy during conventional WBI (25 fractions of 2 Gy WBI, 25 fractions of 2.4 Gy SIB) result in a 2 Gy ED of 66.4 Gy; and
- SIB treatment with single doses of 3.2 Gy within a hypofractionated WBI schedule (15 fractions of 2.7 Gy WBI, 15 fractions of 3.2 Gy SIB) result in a 2 Gy ED of 59.5 Gy.

Compared to the pre1950s standard of a 16 Gy boost as currently used, this calculation model would therefore predict a similar probability of fibrosis for a SIB application during normofractionated WBI as well as in the exemplary hypofractionated schedule. However, conceiving lower “real” α/β values, the probability of detrimental effects for any kind of SIB technique on normal tissue may increase. Furthermore, these assumptions are merely comparing single and total doses, but do not account for possible time factors of shorter RT schedules.

Apart from dose considerations, the absolute boost volume is also predictive for the development of a late fibrosis, with increasing incidence along larger volumes, as reported in a long-term subpopulation analysis of the EORTC-22881 study: “boost versus no-boost” [7]. Prior to this publication, the investigators' group had described worse cosmetic results for boost volumes $>200 \text{ cm}^3$ (significant in univariate analysis; [21]).

The choice of an appropriate EBRT technique to achieve a SIB effect is of further concern. An uncritical application of multifield IMRT techniques is highly problematic, since integral doses outside the PTV should be kept as low as possible in order to diminish stochastic tumor induction effects [4, 18]. Dose intensity modulations should therefore preferably be performed within the tangential beam

arrangements (field-in-field techniques, “tangential” IMRT). It is assumed that after multifield or rotational SIB-IMRT, the subsequent risk of ipsilateral lung cancer induction rises significantly in comparison to a tangential beam design [8].

Clinical evidence of SIB techniques for breast cancer

A further Dutch institution reported a similar experience, with a cohort comprising 1274 patients treated between 2007 and 2009 (28 fractions of 1.8 Gy WBRT, 2.3 Gy SIB; [14]). To date, there has been no information published on toxicities and tumor-related parameters. However, the authors emphasized the necessity for continuous dose planning optimization during a SIB-RT to account for shrinking seroma when exceeding initial sizes of 30 cm³. This was relevant for about 9% of all patients, out of these 77% received plan adaptations to avoid excess treatment volumes during SIB. These findings were recently corroborated by a Chinese group [24].

SIB during hypofractionated WBI (HF-SIB)

Chadha et al. [5] published their first experience in acute toxicity for SIB application during hypofractionated RT in comparison with WBI plus boost in normofractionation: 50 patients were treated by 15 fractions of 2.7 Gy whole-breast and concomitantly 3 Gy tumor bed dose, respectively, whereas 74 patients received 26 fractions of 1.8 Gy WBI followed by 7 fractions of 2 Gy to the tumor bed. No information was given on boost volumes. Concerning acute toxicity 8 weeks after the end of RT, hypofractionated SIB patients experienced significantly less grade ≥ 2 fibroses ($p=0.0015$) and breast pain.

One of the rare long-term reports following HF-SIB was published by Freedman et al. [10]: 75 patients were irradiated in 20 fractions at 2.25 Gy whole-breast and 2.8 Gy tumor-bed dose, respectively. The mean CTV size of the tumor bed amounted to 24 cm³ (range 3–123 cm³). After a median follow-up of 69 months, three local recurrences were noted (5-year LRR 2.7%). Cosmetic as well as function-

al scores were reported as comparable to standard treatment. A volume-based analysis of their findings was not provided.

A recent prospective randomized study from Belgium [20] compares a standard WBI (25 fractions of 2 Gy tangential fields, 8 fractions of 2 Gy electron boost) to a hypofractionated tomotherapy comprising a SIB (15 fractions of 2.8 Gy WBI; 3.4 Gy SIB). Included were 41 patients after BCS and 28 patients following mastectomy. Study endpoint was the occurrence of cardiopulmonary toxicity in dependency from the RT method. After 2 years, the authors described a two-fold skin reaction rate (grade ≥ 1) in the standard treatment arm compared to the tomotherapy cohort (60 vs. 30%), which is however most probably attributable to the electron boost. There was no differentiation along type of operation (breast conservation or mastectomy), nor did the authors report on tissue fibrosis and cosmesis. Cardiac function (LVEF) was not affected by radiation technique; lung function (FEV1) was reported to be less impaired after SIB tomotherapy.

Ongoing studies

The IMPORT HIGH Trial [6] tests the hypothesis whether a risk-adapted dose distribution within the breast during daily dose delivery including a SIB application is capable to reduce late reactions while concomitantly increasing tumor control rates. While the dose is kept lower in zones of assumed minimal residual disease, an increased single dose is pursued in those areas at higher risk for microscopic tumor remnants. Two different HF schedules are tested against a 15 fractions of 2.7 Gy regimen, followed by 8 fractions of 2 Gy boost, which is now considered as standard in the UK. In both investigational arms, a single dose of 2.4 Gy to the whole breast and 2.67 Gy to the index quadrant is prescribed. In the first test cohort, the tumor bed is concomitantly irradiated with 3.2 Gy, whereas the second arm receives 3.5 Gy (isoeffective to 60 and 69 Gy, respectively, towards a 2 Gy fractionation at an assumed α/β value of 3 for late reactions). The study protocol demands for standardization of boost vol-

umes in all treatment arms. There have been no clinical reports up to now.

An US-American randomized phase III trial conducted by the RTOG (1005) investigates patients receiving either sequential or concomitant boosts. In the sequential approach, WBI is offered in normo- as well as hypofractionated RT (25 fractions of 2 Gy and 16 fractions of 2.67 Gy, respectively), followed by 6–7 fractions of 2 Gy tumor bed boost. For (SIB) treatment, WBI is performed in hypofractionation (15 fractions of 2.67 Gy) with a concomitant boost of 3.2 Gy. However, the recruitment goal of 2312 patients lies in the distant future (1/2012: 200 patients).

Conclusion

The proposed SIB strategies in adjuvant radiotherapy during BCT are of high investigational potential. However, the published data are too inconclusive and premature to permit a solid prediction of long-term outcome in terms of tumor control, fibrosis, and cosmesis. From the calculations presented above, the use of SIB techniques with single tumor bed doses of 2.1 Gy for low-risk tumors up to 2.25 Gy for constellations with higher risk for local recurrence seem to be within the therapeutic range. Further evaluation in prospective trials is the preferential tool to clarify these open issues. Dose modulation should preferably be performed within the tangential beam arrangement (field-in-field techniques, “tangential” IMRT) instead of multifield or rotational IMRT. Boost volumes have to be kept as small as possible without compromising oncological requirements and a detailed documentation is imperative. In case of a distinct seroma after tumorectomy (>30 cm³) prior to RT, the necessity of re-planning has to be considered after the first two treatment weeks. For quality assurance and also forensic aspects, long-term follow-up and a meticulous documentation of late effects by an experienced radio-oncologist are mandatory. This is even more important outside clinical trials, as the embedment into a defined observation schedule may be less strict than for study patients. In the absence of analyses of ongoing randomized prospective studies, the breast cancer expert panel of the German Society

of Radiation Oncology (DEGRO) explicitly discourages the routine use of higher SIB fraction sizes as well as the application of SIB during hypofractionated WBI schedules outside clinical trials.

Summary for clinical practice

- Regarding radiobiological considerations, normofractionated SIB seems to be in the therapeutic range, however, prospective data for long-term toxicity are not yet available.
- Normofractionated WBI plus sequential boost remains standard treatment, hypofractionated WBI plus sequential, normofractionated boost is an alternative for selected patients.
- Hypofractionated WBI plus SIB is discouraged outside clinical trials.
- Combination of SIB plus sequential boost is not recommended in the absence of respective data.
- Whenever modifications of the standard technique are used, an increase of normal tissue dose (especially lung, heart and contralateral breast) has strictly to be avoided.
- Long-term observation and documentation are mandatory.

Corresponding address

Prim. Univ.-Prof. Dr. F. Sedlmayer

Department of Radiotherapy and Radiation Oncology, LKH Salzburg,
Paracelsus Medical University Hospital
Muellner Hauptstrasse 48, Salzburg
Austria
F.Sedlmayer@salk.at

Conflict of interest. On behalf of all authors, the corresponding author states that there are no conflicts of interest.

References

1. Bantema-Joppe EJ, Schilstra C, deBock GH et al (2012) Simultaneous integrated boost irradiation after breast-conserving surgery: physician-rated toxicity and cosmetic outcome at 30 months' follow-up. *Int J Radiat Oncol Biol Phys* 83:e471–477
2. Bantema-Joppe EJ, van der Laan HP, de Bock GH et al (2011) Three-dimensional conformal hypofractionated simultaneous integrated boost in breast conserving therapy: results on local control and survival. *Radiother Oncol* 100:215–220
3. Bentzen SM, Yarnold JR (2010) Reports of unexpected late side effects of accelerated partial breast irradiation—radiobiological considerations. *Int J Radiat Oncol Biol Phys* 77:969–973
4. Baack T, Wenz F (2012) Secondary cancers after radiotherapy may appear early and atypical. *Strahlenther Onkol* 188:91–92; author reply 92–93
5. Chadha M, Vongtama D, Friedmann P et al (2012) Comparative acute toxicity from whole breast irradiation using 3-week accelerated schedule with concomitant boost and the 6.5-week conventional schedule with sequential boost for early-stage breast cancer. *Clin Breast Cancer* 12:57–62
6. Coles C, Yarnold J (2006) IMPORT Trials Management Group. The IMPORT trials are launched. *Clin Oncol (R Coll Radiol)* 18:587–590
7. Collette S, Collette L, Budiharto T et al (2008) Predictors of the risk of fibrosis at 10 years after breast conserving therapy for early breast cancer: a study based on the EORTC Trial 22881-10882 "boost versus no boost". *Eur J Cancer* 44:2587–2599
8. Donovan EM, James H, Bonora M et al. (2012) Second cancer incidence risk estimates using BEIR VII models for standard and complex external beam radiotherapy for early breast cancer. *Med Phys* 39:5814–5824
9. Fowler JF (1992) Brief summary of radiobiological principles in fractionated radiotherapy. *Sem Radiat Oncol* 2:16–21
10. Freedman GM, Anderson PR, Bleicher RJ et al (2012) Five-year local control in a phase II study of hypofractionated intensity modulated radiation therapy with an incorporated boost for early stage breast cancer. *Int J Radiat Oncol Biol Phys* 84:888–893
11. Freedman GM, Anderson PR, Goldstein LJ, et al (2007) Four-week course of radiation for breast cancer using hypofractionated intensity modulated radiation therapy with an incorporated boost. *Int J Radiat Oncol Biol Phys* 68:347–353
12. Goldsmith C, Haviland J, Tsang Y et al (2011) Large breast size as a risk factor for late adverse effects of breast radiotherapy: is residual dose inhomogeneity, despite 3D treatment planning and delivery, the main explanation? *Radiother Oncol* 100:236–240
13. Hurkmans CW, Dijkmans I, Reijnen M et al (2012) Adaptive radiation therapy for breast IMRT-simultaneously integrated boost: three-year clinical experience. *Radiother Oncol* 103:183–187
14. Hurkmans CW, Meijer GJ, van Vliet-Vroegindeweij C et al (2006) High-dose simultaneously integrated breast boost using intensity-modulated radiotherapy and inverse optimization. *Int J Radiat Oncol Biol Phys* 66:923–930
15. Jagsi R, Ben-David MA, Moran JM et al. (2010) Unacceptable cosmesis in a protocol investigating intensity-modulated radiotherapy with active breathing control for accelerated partial-breast irradiation. *Int J Radiat Oncol Biol Phys* 76:71–78
16. Moody AM, Mayles WP, Bliss JM et al (1994) The influence of breast size on late radiation effects and association with radiotherapy dose inhomogeneity. *Radiother Oncol* 33:106–112
17. Mukesh M, Harris E, Jena R et al (2012) Relationship between irradiated breast volume and late normal tissue complications: a systematic review. *Radiother Oncol* 104:1–10
18. Nestle-Krämling C, Bölke E, Budach W et al (2011) [Hemangiosarcoma after breast-conserving therapy of breast cancer: report of four cases with molecular genetic diagnosis and literature review]. *Strahlenther Onkol* 187:656–664
19. Sautter-Bihl ML, Budach W, Dunst J et al (2007) DEGRO Practical Guidelines for Radiotherapy of Breast Cancer I. Breast-Conserving Therapy. *Strahlenther Onkol* 183:661–666
20. Van Parijs H, Miedema G, Vinh-Hung V et al (2012) Short course radiotherapy with simultaneous integrated boost for stage I–II breast cancer, early toxicities of a randomized clinical trial. *Radiation Oncology* 7:80
21. Vrieling C, Collette L, Fourquet A et al (2000) The influence of patient, tumor and treatment factors on the cosmetic results after breast-conserving therapy in the EORTC "boost versus no boost" trial. *EORTC Radiotherapy and Breast Cancer Cooperative Groups. Radiother Oncol* 55:219–232
22. Whelan T, Pignol JP, Levine MN et al (2010) Long-term results of hypofractionated radiation therapy of breast cancer. *NEJM* 362:513–520
23. Yang Z, Chen J, Xie J, et al. (2012) Simultaneous Integrated Boost in Breast Conserving Radiotherapy: Is Replanning Necessary Following Tumor Bed Change? *Technol Cancer Res Treat* Oct 19 (Epub ahead of print)
24. Yarnold J, Ashton A, Bliss J et al (2005) Fractionation sensitivity and dose response of late adverse effects in the breast after radiotherapy for early breast cancer: Long – term results of a randomised trial. *Radiother Oncol* 75:9–17