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EDITORIAL

Personalized radiotherapy for invasive breast cancer in 2017

National S3 guidelines and DEGRO and AGO recommendations

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Radiotherapy in the curative setting for breast cancer has evolved over the past 15 years, from a one size fits all approach to a personalized, risk-adapted treatment within a multidisciplinary environment, taking more and more patient factors, the biology of the tumor, and the extent of disease in the lymph nodes into account. Before the year 2000, the picture was straightforward, with no radiotherapy following mastectomy (postmastectomy radiotherapy, PMRT), and whole breast radiotherapy (WBRT) with 50 Gy over 5 weeks after breast-conserving surgery in all patients. The picture is more complex today (see Fig. 1).

Postmastectomy radiotherapy

The Danish and British Columbia trials [1–3] identified pre- and postmenopausal patients with locally advanced tumors (T3-4Nx or TxN+) for whom an overall survival benefit was achieved by postmastectomy radiotherapy (PMRT) of 50 Gy. The initial consensus was that patients with four and more positive nodes benefitted the most in terms of overall survival; however, a recent analysis by the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) [4] underlined that patients with one to three positive nodes also showed a consistent benefit, particularly when chemotherapy was given. This benefit is substantial in high-risk patients (G3, triple negative, lymph vascular invasion, Her2 positive, or age <40 years) [5]. One should keep in mind that all patients included in the EBCTCG analysis received PMRT to the chest wall and regional nodal irradiation (RNI; medial supraclavicular and mostly mammary internal). On the other hand, there was a lack of consistent benefit for all T3N0 patients. Meta-analyses have identified subgroups of the T3N0 category with risk factors, e. g., large tumor, young age, high grading, lymph vessel invasion, and triple negative, which may still show a benefit based on the individual risk assessment, particularly when two or more risk factors are positive [6, 7].

Concerning the situation after neoadjuvant chemotherapy, there is still a paucity of data regarding the indication for PMRT. Therefore, the initial clinical staging before neoadjuvant chemotherapy is used until ongoing prospective studies have reported results (e. g., NSABP B 51).

In summary, PMRT is currently recommended in patients with T4 or N+ disease, or following R+ resection. PMRT can be avoided following R0 mastectomy in T1–2N0 patients and in T3N0 patients without risk factors. Typically, PMRT should include the chest wall and the regional nodal areas [7].

Radiotherapy and breast-conserving surgery

Radiotherapy is an integral part of the breast-conserving therapy approach. If at all, no radiotherapy following breast conserving surgery (BCS) may be an option for patients

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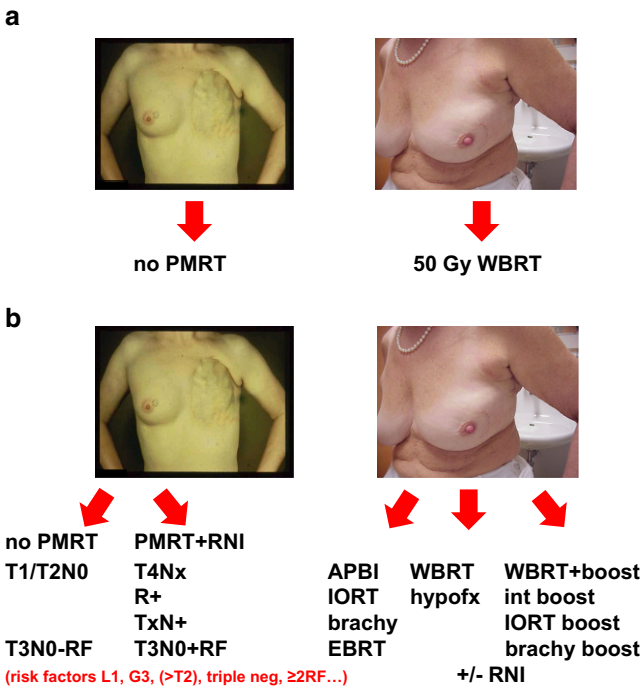

Fig. 1 Adjuvant radiotherapy for breast cancer; **a** before 2000, **b** in 2017. *PMRT* postmastectomy radiotherapy, *WBRT* whole breast radiotherapy, *RNI* regional nodal irradiation, *APBI* accelerated partial breast irradiation, *IORT* intraoperative radiation therapy, *brachy* brachytherapy, *EBRT* external beam radiotherapy, *Int* integrated, *RF* risk factors

whose life expectancy is shorter than 10 years, with hormone receptor-positive T1N0 tumors without Her2neu overexpression. Patients have to be counselled that even with rigorous antihormonal therapy, there is a considerably increased risk for local recurrence (CALBG, BASO2, PRIME II trials: 4–6% local recurrence without radiotherapy after 5 years for patients above 70/65/65 years of age with receptor-positive T1N0 tumors; non-grade III; for a summary see [8, 9]).

Based on long-term results from three randomized studies, (accelerated) partial breast irradiation ((A)PBI) using intraoperative radiotherapy or postoperative multicatheter brachytherapy or external beam radiotherapy is an option for postmenopausal patients with low-risk tumors (T1N0, R0 resection, hormone receptor positive, non-lobular histology). Participation in a clinical study is recommended for patients between 50 and 70 years of age [10–12].

Fractionated WBRT is the standard of care for the overwhelming majority of patients following BCS. Hypofractionated WBRT, i. e., the application of single doses larger than 2 Gy up to reduced total doses, e. g., 15–16 fractions of 2.66 Gy, has been shown in large randomized trials with sufficient follow-up to be at least as effective in terms of local tumor control as conventionally fractionated radiotherapy and results in significantly less acute and late effects [13–15]. Consequently, hypofractionated radiotherapy is the preferred radiation schedule in patients who do not need radiotherapy of regional lymph nodes. In younger and high-risk patients, a sequential boost of 10–16 Gy to the tumor bed is recommended, although the improvement in local control is modest and there was no overall survival benefit in long-term follow-up [16, 17].

Based on the PMRT data, two recent randomized trials (MA20, EORTC), and a Danish cohort study [18–20], the indication for RNI was expanded following BCS [21–23]. Depending on the number of positive nodes (>3, 1–3, 0 but high risk), the strength of the recommendation to include the supraclavicular/medial axillary region decreases in AGO (++, +, +/–) and in S3 (have to/should/can). In most of the cases where RNI is indicated, irradiation of the internal mammary nodes should be considered (for a detailed analysis see [23]). Typically, conventional fractionation is used when RNI is given following BCS. Based on the AMOROS trial, it is obvious that RNI yields lower rates of side effects following sentinel node biopsy compared to radical axillary dissection [24].

Conclusion

This short overview summarizes the current developments in risk-adapted radiotherapy for breast cancer. One has to keep in mind that the different guideline committees come to slightly different conclusions depending on the composition of their membership and the process of literature collection and interpretation [25–27].

Conflict of interest F. Wenz and W. Budach declare that they have no competing interests.

References

1. Overgaard M, Hansen PS, Overgaard J, Rose C, Andersson M, Bach F, Kjaer M, Gadeberg CC, Mouridsen HT, Jensen MB, Zedeler K (1997) Postoperative radiotherapy in high-risk premenopausal women with breast cancer who receive adjuvant chemotherapy. Danish Breast Cancer Cooperative Group 82b Trial. N Engl J Med 337(14):949–955
2. Overgaard M, Jensen MB, Overgaard J, Hansen PS, Rose C, Andersson M, Kamby C, Kjaer M, Gadeberg CC, Rasmussen BB, Blichert-Toft M, Mouridsen HT (1999) Postoperative radiotherapy in high-risk postmenopausal breast-cancer patients given adjuvant tamoxifen: Danish Breast Cancer Cooperative Group DBCG 82c randomised trial. Lancet 353(9165):1641–1648
3. Ragaz J, Jackson SM, Le N, Plenderleith IH, Spinelli JJ, Basco VE, Wilson KS, Knowling MA, Coppin CM, Paradis M, Coldman AJ, Olivotto IA (1997) Adjuvant radiotherapy and chemotherapy in node-positive premenopausal women with breast cancer. N Engl J Med 337(14):956–962
4. Early Breast Cancer Trialists' Collaborative Group (2014) Effect of radiotherapy after mastectomy and axillary surgery on 10-year recurrence and 20-year breast cancer mortality: meta-analysis of

individual patient data for 8135 women in 22 randomised trials. Lancet 383(9935):2127–2135
5. Li Y, Moran MS, Huo Q, Yang Q, Haffty BG (2013) Post-mastectomy radiotherapy for breast cancer patients with t1-t2 and 1–3 positive lymph nodes: a meta-analysis. PLOS ONE 8(12):e81765
6. Recht A, Comen EA, Fine RE, Fleming GF, Hardenbergh PH, Ho AY, Hudis CA, Hwang ES, Kirshner JJ, Morrow M, Salerno KE, Sledge GW Jr, Solin LJ, Spears PA, Whelan TJ, Somerfield MR, Edge SB (2016) Postmastectomy radiotherapy: An American Society of Clinical Oncology, American Society for Radiation Oncology, and Society of Surgical Oncology Focused Guideline Update. J Clin Oncol 34(36):4431–4442
7. Wenz F, Sperk E, Budach W et al (2014) DEGRO practical guidelines for radiotherapy of breast cancer IV: radiotherapy following mastectomy for invasive breast cancer. Strahlenther Onkol 190(8):705–714
8. Matuschek C, Bölke E, Haussmann J, Mohrmann S, Nestle-Krämling C, Gerber PA, Corradini S, Orth K, Kammers K, Budach W (2017) The benefit of adjuvant radiotherapy after breast conserving surgery in older patients with low risk breast cancer – a meta-analysis of randomized trials. Radiat Oncol 12(1):60
9. Vaidya JS, Bulsara M, Wenz F, Joseph D, Saunders C, Massarut S, Flyger H, Eiermann W, Alvarado M, Esserman L, Falzon M, Brew-Graves C, Potyka I, Tobias JS, Baum M, TARGIT trialists' group (2015) Pride, prejudice, or science: attitudes towards the results of the TARGIT-A trial of targeted Intraoperative radiation therapy for breast cancer. Int J Radiat Oncol Biol Phys 92:491–497
10. Strnad V, Ott OJ, Hildebrandt G, Kauer-Dorner D, Knauerhase H, Major T, Lyczek J, Guinot JL, Dunst J, Gutierrez Miguelez C, Slampa P, Allgäuer M, Lössl K, Polat B, Kovács G, Fischedick AR, Wendt TG, Fietkau R, Hindemith M, Resch A, Kulik A, Arribas L, Niehoff P, Guedea F, Schlamann A, Pötter R, Gall C, Malzer M, Uter W, Polgár C, Groupe Européen de Curiethérapie of European Society for Radiotherapy and Oncology (GEC-ESTRO) (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
11. Vaidya JS, Wenz F, Bulsara M, Tobias JS, Joseph DJ, Keshtgar M, Flyger HL, Massarut S, Alvarado M, Saunders C, Eiermann W, Metaxas M, Sperk E, Sütterlin M, Brown D, Esserman L, Roncadin M, Thompson A, Dewar JA, Holtveg HM, Pigorsch S, Falzon M, Harris E, Matthews A, Brew-Graves C, Potyka I, Corica T, Williams NR, Baum M, TARGIT trialists' group (2014) Risk-adapted targeted intraoperative radiotherapy versus whole-breast radiotherapy for breast cancer: 5-year results for local control and overall survival from the TARGIT – A randomised trial. Lancet 383(9917):603–613
12. Livi L, Meattini I, Marrazzo L, Simontacchi G, Pallotta S, Saieva C, Paiar F, Scotti V, De Luca Cardillo C, Bastiani P, Orzalesi L, Casella D, Sanchez L, Nori J, Fambrini M, Bianchi S (2015) Accelerated partial breast irradiation using intensity-modulated radiotherapy versus whole breast irradiation: 5-year survival analysis of a phase 3 randomised controlled trial. Eur J Cancer 51(4):451–463
13. Whelan TJ, Pignol J-P, Levine MN et al (2010) Long-term results of hypofractionated radiation therapy for breast cancer. N Engl J Med 362(6):513–520
14. Haviland JS, Owen JR, Dewar JA et al (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 14:1086–1094
15. Hickey BE, James ML, Lehman M, Hider PN, Jeffery M, Francis DP, See AM (2016) Fraction size in radiation therapy for breast conservation in early breast cancer. Cochrane Database Syst Rev 7:CD003860
16. Bartelink H, Maingon P, Poortmans P, Weltens C, Fourquet A, Jager J, Schinagl D, Oei B, Rodenhuis C, Horiot JC, Struikmans H, Van Limbergen E, Kirova Y, Elkhuizen P, Bongartz R, Miralbell R, Morgan D, Dubois JB, Remouchamps V, Mirimanoff RO, Collette S, Collette L, European Organisation for Research and Treatment of Cancer Radiation Oncology and Breast Cancer Groups. (2015) Whole-breast irradiation with or without a boost for patients treated with breast-conserving surgery for early breast cancer: 20-year follow-up of a randomised phase 3 trial. Lancet Oncol 16(1):47–56
17. Sedlmayer F, Sautter-Bihl ML, Budach W et al (2013) DEGRO practical guidelines: radiotherapy of breast cancer I: radiotherapy following breast conserving therapy for invasive breast cancer. Strahlenther Onkol 189(10):825–833
18. Whelan TJ, Olivotto IA, Parulekar WR et al (2015) Regional nodal irradiation in early-stage breast cancer. N Engl J Med 373(4):307–316
19. Poortmans PM, Collette S, Kirkove C et al (2015) Internal mammary and medial supraclavicular irradiation in breast cancer. N Engl J Med 373(4):317–327
20. Thorsen LB, Offersen BV, Dano H et al (2016) DBCG-IMN: a population-based cohort study on the effect of internal mammary node irradiation in early node-positive breast cancer. J Clin Oncol 34(4):314–320
21. Budach W, Kammers K, Boelke E, Matuschek C (2013) Adjuvant radiotherapy of regional lymph nodes in breast cancer – a meta-analysis of randomized trials. Radiat Oncol 8(1):267
22. Budach W, Bolke E, Kammers K et al (2015) Adjuvant radiation therapy of regional lymph nodes in breast cancer – a meta-analysis of randomized trials- an update. Radiat Oncol 10:258
23. Sautter-Bihl ML, Sedlmayer F, Budach W, Dunst J, Feyer P, Fietkau R, Fussl C, Haase W, Harms W, Piroth MD, Souchon R, Wenz F, Sauer R (2014) DEGRO practical guidelines: radiotherapy of breast cancer III-radiotherapy of the lymphatic pathways. Strahlenther Onkol 190(4):342–351
24. Donker M, van Tienhoven G, Straver ME et al (2014) Radiotherapy or surgery of the axilla after a positive sentinel node in breast cancer (EORTC 10981–22023 AMAROS): a randomised, multicentre, open-label, phase 3 non-inferiority trial. Lancet Oncol 15(12):1303–1310
25. AGO (2017) Empfehlungen gynäkologische Onkologie Kommission Mamma. http://www.ago-online.de/de/infothek-fuer-aerzte/leitlinienempfehlungen/mamma/. Accessed May 11, 2017
26. AWMF (2012) Leitlinien-Detailansicht Mammakarzinom der Frau; Diagnostik, Therapie und Nachsorge (Version 2012). http://www.awmf.org/leitlinien/detail/ll/032-045OL.html. Accessed May 11, 2017
27. Krug D, Baumann R, Budach W, Dunst J, Feyer P, Fietkau R, Haase W, Harms W, Piroth MD, Sautter-Bihl ML, Sedlmayer F, Souchon R, Wenz F, Sauer R, Breast cancer expert panel of the German Society of Radiation Oncology (DEGRO) (2017) Current controversies in radiotherapy for breast cancer. Radiat Oncol 12(1):25