Challenges in Radiotherapy

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Question 1: What Treatment Do You Recommend after Complete Pathological Response after Neoadjuvant Chemotherapy in Initially Node Positive Breast Cancer (Biopsy Proven vs. Clinically Only)? Which Risk Factors Do You Take into Account for Your Decision in Favor of Postoperative Radiotherapy?

Fastner: Up to now, there existed no clinical evidence to omit adjuvant locoregional radiotherapy (RT) of initial node positive (cN+) breast cancer patients, who develop a pathological complete response after neoadjuvant chemotherapy (NAC) followed by surgery [1, 2]. This seems to be independent from whether cN+ is histologically confirmed by biopsy or described according to radiological investigation only (ultrasound, MRT). However, if there remains uncertainty how to classify the clinical nodal status, either into cN0 or cN+, a consecutive node biopsy is desirable [1]. In terms of breast-conserving surgery (BCS) and axillary dissection (level I/II), RT should be given to the whole breast and at least supra/infraclavicular nodes. Dependent on an individual case-by-case basis, regional node irradiation (RNI) should be expanded to axillary (insufficient axillary dissection, sentinel lymph node biopsy only) [3] or parasternal nodes (medial/central tumor location and/or at least 3 clinical positive nodes) [4, 5], respectively. After mastectomy and axillary dissection, the indication for locoregional irradiation

(chest wall and regional nodes) should be set in dependency of the initial clinical tumor stage and the presence of one or more risk factors [6, 7]. Hence, a premenopausal status, high-grade tumors (G3), a negativity for hormonal receptors or positivity for Her2neu, medial/central tumor localization, lymphovascular invasion (L1) and Ki-67 >30%, either separately or in combination, should be taken into consideration for decision-making whether or not to irradiate in a specific case.

Krug: Unfortunately, there are no data from prospective randomized controlled trials to answer this question. There are two treatment decisions, which merit consideration: RNI and postmastectomy RT (PMRT). A recent systematic review showed that there are only few retrospective studies addressing the use of treatment response to NAC to guide decision-making regarding adjuvant RT in these two specific situations [1]. In general, PMRT and RNI were beneficial especially in patients with clinical stage III disease, even in the context of pathological complete response. However, data were conflicting in patients with stage II disease (i.e., T1–2 N1). I believe that PMRT and RNI should be standard in patients with clinical stage III disease and should be offered to all patients with clinical stage II disease in the presence of further risk factors, such as grade 3, triple negative breast cancer, age <40 years. Suspicious lymph nodes should be histologically evaluated before initiation of treatment in all patients.

Matuschek: Adjuvant RT of the breast/chest wall and regional lymph node region (≥ 3 positive sentinel lymph nodes) after complete pathological response is recommended in the presence of high-risk factors including premenopausal hormonal status, central or medial tumor localization, high tumor grade (G2–3) and negativity for hormonal receptors.

Meattini: There is still no consensus on the use of postoperative RT in case of pathological complete response after NAC. In the largest reported analysis of RT for clinical N1 patients treated with NAC, PMRT was associated with improved overall survival for all pathological nodal subgroups, while no overall survival differences were observed with the addition of RNI to breast RT [8]. Several independent predictors of local relapse (LR) after BCS or mastectomy were identified, such as age, clinical nodal status (before NAC), and pathological nodal status/breast tumor response. By using these independent predictors, risk groups of patients could be identified and used to predict LR risk and to optimize the use of adjuvant RT [9].

In our institution, we do not routinely irradiate the chest wall or residual breast plus RNI after BCS or mastectomy in case of pathological complete response after NAC. However, we evaluate all patients who are candidates for NAC due to node positivity (both biopsy proven or clinically) for postoperative RT. For instance, we strongly recommend discussing each patient in a multidisciplinary tumor board, both pre- and postoperatively. Main characteristics to consider are initial burden of disease in the nodal regions and the breast (i.e., clinical stage III, cN2), age of patients (i.e., age less than 40 years), and tumor biology (i.e., triple negative, HER2-positive).

However, there is a lack of evidence from randomized trials, and major ongoing trials (i.e., NSABP B-51/RTOG 1304, Alliance 011202 trial) will answer many important questions, but additional issues will need to be addressed. Present consensus guidelines are based on retrospective studies or extrapolated data in the absence of level I evidence. Therefore, the ideal approach should be to enroll eligible patients in clinical trials.

Question 2: Should the Internal Mammary Lymphatics Always Be Included in the Radiotherapy Volumes of Node Positive Breast Cancer Patients? Based on which Factors Do You Decide to Treat the Infra-/Supraclavicular Lymph Nodes Only and when Do You Include the Internal Mammary Nodes?

Fastner: For patients with positive lymph nodes, RNI to the supra-/infraclavicular (SCV) and/or internal mammary region has shown to be beneficial with regard to

survival end point analyses [9]. For a treatment decision, the following criteria should be evaluated: the number of affected lymph nodes (1–3 vs. ≥ 4), tumor localization within the breast (central/inner or outer quadrants), tumor grade (intermediate to high or low grade), hormonal receptor status (positive or negative), and menopausal status (pre- or postmenopausal). The risk factor ≥ 4 positive lymph nodes on its own, or 1–3 positive lymph nodes together with a central/inner tumor localization, RNI should be administered to both supraclavicular and internal mammary lymph nodes (IMN), respectively [10]. In all other cases dependent on tumor localization and at least two other risk factors (premenopausal status, negative hormonal receptors, intermediate or high tumor grading) RNI is considered for supraclavicular lymph nodes only.

Krug: Improvement of distant recurrence-free and disease-free survival has only been shown in trials which targeted the IMN along with the SCV lymphatic drainage [4, 10, 11]. Thus, I believe that the IMN should be treated, whenever improvement of these oncological end points is the goal. RNI may be used in patients with positive sentinel lymph node biopsy as an alternative to axillary dissection. The AMAROS trial did show similar axillary recurrence rates for RNI to the full axilla (level I–III) and the SCV lymph nodes as compared to axillary dissection in this setting [3]; however, lymph edema rates were cut in half with RNI.

Currently, there is no clear definition of prognostic or predictive factors that may guide the target definition in this situation. I would use comprehensive RNI including the IMN in patients with biologically aggressive tumors (triple negative breast cancer, high tumor grade), in patients with 4 or more involved lymph nodes and in patients with medial/central tumor location irrespective of the number of involved lymph nodes. In patients with positive sentinel lymph node biopsy without further risk factors, I would not treat the IMN. I do not routinely use RNI in node-negative patients. Whenever targeting the IMN, constraints for lung and heart should be carefully examined [12].

Matuschek: In the case of ≥ 3 positive lymph nodes we indicate lymph node irradiation of the supra/infraclavicular lymphatic pathways and include the internal mammary lymphatic pathways in case of G2–3- or ER/PgR-negative tumors. In patients with 1–3 positive lymph nodes, we irradiate the SCV lymph node region when other high-risk factors are present: central or medial tumor localization and G2–3- or ER/PgR-negative or premenopausal patients with lateral localized breast cancer and G2–3 or ER/PgR-negative ones. The indication for RNI of the IMN pathway is the same in case of 1–3 posi-

tive lymph nodes, so we treat SCV and the IMN pathways as a package. We avoid irradiating the IMN pathway in case of systemic therapy with trastuzumab or in patients with high cardiac risk factors.

Meattini: In our institution we do not routinely irradiate IMN, except for cases where pre- or postoperative imaging shows IMN positivity or suspect lymph nodes. However, it has been recently demonstrated that the benefit of RNI including IMN for selected high-risk patients, with a marginal effect on overall survival but an improved disease-free, distant disease-free, and breast cancer-specific survival [4]. Major features to be considered should be: tumor biology, the dominant site of the breast lesion (i.e., medial localization), pathological T stage (i.e., pT2), and N stage (i.e., pN2). Therefore, the indication should always be discussed in a multidisciplinary team, considering also other postoperatively planned treatments.

Question 3: Should Patients with Ductal Carcinoma in situ Always Receive Postoperative Radiotherapy following Breast-Conserving Surgery? What Is Your Clinical Practice in Your Country?

Cutuli: In France, the national guidelines published in 2012 recommended postoperative RT after BCS for ductal carcinoma in situ (DCIS). In 2 large surveys, the rates of patients treated by RT after BCS were 89% (2003–2004) and 96% (2014–2015) [13]. Indeed, 4 randomized trials and meta-analyses, as well as several other studies, showed a 50–60% reduction of local recurrences (both in situ and invasive) with whole-breast irradiation (WBI; 50 Gy or equivalent dose).

Furthermore, even in extremely selected studies (ECOG-5194, RTOG-9804 [14]) for “very low-risk DCIS,” the long LR rates are not negligible. Moreover, in case of invasive LR, approximately 12% of the patients developed long-term metastases. The RT omission should be debated in women older than 60 years with very small grade I DCIS, free margins (≥ 3 mm), and favorable biological profile (e.g., positive HR, low Ki-67), such as proposed in a new “de-escalation” trial launched in France (ROMANCE Trial).

Fastner: According to the last meta-analysis of the early breast cancer trialists’ collaborative group (EBCTCG) RT after BCS of DCIS halves the probability for breast recurrences in every risk group [15]. However, some controversy exists whether RT is mandatory in an exclusively low-risk constellation, like small tumor sizes (<2.5 cm), low-grade differentiation (G1–2), and >60 years of age [16] which has been shown to be beneficial

in terms of local control by the RTOG-9804 trial [14], respectively. Therefore, we are offering RT to all DCIS patients after BCS. Omission of RT should only be considered for frail elderly patients with a short expectancy of life.

Krug: I think that postoperative RT for patients with low-risk DCIS (tumor size <2.5 cm, G1/2, margins >2 mm, age >60 years) should be discussed on a case-by-case basis. In the absence of a survival benefit and with a number needed to treat of around 12 for prevention of a DCIS recurrence and 25 for prevention of invasive recurrence [17], some of these women may opt to omit adjuvant RT. However, individual life expectancy, comorbidities, patient preferences and planned endocrine therapy as well as the excellent tolerability of adjuvant RT in the current era have to be considered [18]. In my experience, most women with DCIS have a strong wish for safety and choose to receive adjuvant RT. Nevertheless, shared decision-making and thorough communication of risks and benefits are crucial in this situation.

Matuschek: RT reduces the risk for a local recurrence significantly in DCIS but does not have any impact on overall survival. Especially in low-risk situations, we discuss the individual advantages and disadvantages of RT with every patient.

Meattini: RT reduces the absolute 10-year risk of any ipsilateral breast event (i.e., either recurrent DCIS or invasive cancer), and it is effective regardless of the age at diagnosis, extent of BCS, use of tamoxifen, method of DCIS detection, final surgical margin (FSM) status, focality, grade, comedonecrosis, architecture, or tumor size [15]. Moreover, this benefit persists over time [19, 20].

In our institution most patients still receive postoperative RT after BCS. It is well known that several patient-, tumor-, and treatment-related features significantly impact on LR risk [21]. Most patients with FSM less than 1 mm undergo re-excision. Therefore, the use of boost is not routinely performed since its ability to overcome the unfavorable effect of an unsatisfactory FSM is not clear [22]. The vast majority of patients did not receive an adjuvant endocrine therapy, since its benefit is less clear and robust as compared to adjuvant RT [23, 24].

However, a very-low-risk group of patients exists, for whom a de-escalation approach should be tested (i.e., radiation omission, partial breast RT). Since reliable and validated prognostic scores do still not exist [25, 26], a clinical trial context is preferable.

Question 4: Is the Hypofractionated Treatment Approach after Breast-Conserving Surgery Standard of Care in Your Country? Do You Apply Hypofractionation Also in the Treatment of Ductal Carcinoma in situ, after Mastectomy or in the Treatment of the Lymphatic Pathways?

Cutuli: Hypofractionated whole-breast RT has been a validated option in France since 2015 (updated National Guidelines). According to international trials, three schemes are recommended, i.e. 42.5 Gy/16 fractions/3 weeks, 40 Gy/15 fractions/3 weeks, or 42 Gy/13 fractions/5 weeks. These RT modalities are preferably applied in postmenopausal patients with pT1T2N0 tumors. In these cases, the indications and modalities of a tumor bed boost remain widely debated. In the daily clinical practice for elderly patients (>70–75 years), a protocol delivering a whole-breast dose of 45 Gy in 15 fractions over 5 weeks (3 fractions per week) is also commonly used. Another scheme developed in Nancy with a “concomitant boost” delivers 50 Gy in 25 fractions over 5 weeks, with twice a week an additional 1 Gy dose to the tumor bed (10 fractions in total, resulting in a whole radiobiological equivalent dose of 66 Gy).

For DCIS, there are no official recommendations, but the results of several Canadian studies (Ontario and Quebec) confirmed the same local control between schemes of 50 Gy/25 fractions/5 weeks and 42.5 Gy/16 fractions/3 weeks. Regarding hypofractionation of the chest wall and/or lymphatic nodes, there are no specific recommendations due to scarce literature data.

Fastner: Hypofractionated WBI (HF-WBI) after BCS has proven to be at least isoeffective compared to conventional fractionation, in terms of local control, acute and late toxicity, for invasive breast cancer and DCIS, respectively [27, 28]. Hence, HF-WBI is recommended as appropriate regimen primarily for patients who are not candidates for additional RNI. After mastectomy, a recently published prospective randomized trial reported no inferior clinical results if the chest wall and the ipsilateral supraclavicular/level III axillary nodes were treated by moderate hypofractionation as compared to conventional standard irradiation [29]. This seems to be also true for hypofractionated RNI alone, if focusing on late reactions like plexopathia, shoulder immobility or arm lymphedema [30, 31]. According to the available data, some controversy exists for a common guideline-based treatment recommendation. However, on an individual case basis, moderate hypofractionated RNI seems possible [32]. On the basis of the current literature, in our institution HF-WBI is offered after BCS for invasive and in situ carcinoma of the breast as well as after mastectomy to the chest wall if indicated. Hypofractionated RNI is not performed outside of clinical trials.

Krug: The German national S3 guidelines recommend hypofractionated RT as the standard of care for postoperative whole-breast RT with the exception of patients receiving RNI [32]. The evidence regarding hypofractionated PMRT and RNI is still limited; however, data from a randomized controlled phase III trial have recently been published and support the use of hypofractionated RT in this setting [29]. I have used hypofractionation in selected patients with DCIS in the past; however, data from 2 randomized controlled phase III trials are still pending (TROC 07.01 (NCT00470236) and Bonbis (NCT00907868)).

Matuschek: Yes, the hypofractionated treatment in invasive breast cancer after BCS is standard of care in most German RT departments. When lymph node regions are included, maybe most departments still use the normofractionated regime. In the S3 guidelines the hypofractionated regime is recommended with more precaution because the hypofractionated irradiated patient group was underrepresented in the randomized trials. In DCIS after BCS we discuss the topic on an individual patient basis.

Meattini: Robust long-term data have demonstrated the noninferiority of HF-WBI as compared to conventional fractionated WBI [33, 34]. Major updated guidelines stated that for women with invasive breast cancer receiving WBI, the preferred dose fractionation scheme is HF-WBI to a dose of 40 Gy in 15 fractions or 42.5 Gy in 16 fractions [35, 36].

HF-WBI is largely diffuse in Italy, although it is still not standard of care. In our institution we apply HF-WBI for all patients undergoing BCS for whom postoperative WBI is indicated, including DCIS patients (40 Gy in 15 fractions) since 2014. When a tumor bed boost is prescribed, it is also hypofractionated (13.3 Gy in 5 fractions or 18.9 Gy in 7 fractions depending on FSM status). Conversely, after mastectomy or in the case of RNI we still use conventional fractionation (50 Gy in 25 fractions), waiting for the results from ongoing studies (i.e., Skagen trial 1, NCT02384733).

Question 5: Do You Perform Partial Breast Irradiation? Which Patients Would You Treat with Partial Breast Irradiation and which Technique and Fractionation Do You Use?

Fastner: Partial breast irradiation (PBI) either with postoperative hypofractionated external beam RT [37] intraoperative [38, 39] or interstitial techniques [40, 41] seems to be an alternative treatment option if patients could be allocated to “very” low-risk breast cancer subtypes [42–44]. In our own institution, intraoperative RT with electrons has had a long tradition administered as

anticipated tumor bed boost since 1998. However, according to international guidelines and recommendations [43, 44], intraoperative RT with electrons as single-shot full-dose treatment (21 Gy at the 90% reference isodose, 23.4 Gy Dmax) is offered exclusively to patients who are classified as “suitable” with unicentric(-focal) Luminal A tumors of sizes <2 cm, negative lymph nodes (cN0 and negative intraoperative frozen section histology for sentinel nodes), ≥50 years of age, clear resection margins, tumor grading G1/2 without neoadjuvant systemic treatment, respectively. Moreover, with lobular histology, preoperative breast MRT is mandatory [45]. Patients with pure DCIS or suspicious for an extensive/or predominant intraductal component and/or genetic high-risk constellation are not considered for PBI.

Krug: I do not routinely use accelerated PBI (APBI) in clinical practice. Nevertheless, I think that APBI may be offered to selected low-risk patients capable of understanding the limitations of the data currently available from randomized controlled trials. From my point of view, the preferred technique would be multicatheter brachytherapy with 8 × 4 Gy based on the excellent results from the GEC-ESTRO trial [41, 46] and the 10-year data from Hungary [47]. If multicatheter brachytherapy is not available, or institutional experience with this technique is limited, I would suggest percutaneous RT with 5 × 6 Gy based on the Florence IMRT trial [48] or with 15 × 2.67 as per the IMPORT LOW trial [37].

Matuschek: Yes, but only in selected cases, especially older patients with low-risk breast cancer. In our breast cancer center intraoperative RT is possible. We discuss the advantages and disadvantages of PBI versus WBI or to omit RT with the patients. We offer 1 × 20 Gy as a single fraction using intraoperative RT. For this procedure lead shielding for protection of the ribs is necessary.

Meattini: Following the published results of main phase III trials [37, 38, 41, 48, 49] we recommend PBI using external beam RT and brachytherapy techniques, in

accordance with the UK consensus statement on postoperative RT for breast cancer [36]. Conversely, intraoperative RT is not recommended due to lack in robustness of published data (i.e., basic statistical assumptions, follow-up at time of publication, patient selection bias) [38, 49–51].

In our Institution we follow the 30 Gy in 5 fractions schedule (6 Gy per fraction, every other day) using an intensity-modulated technique as described in the University of Florence phase III trial [48]. We strongly recommend to select patients by following the PBI ESTRO [40] and ASTRO [44] statements.

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