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Current Trends and Challenges in Real-World Breast Cancer Adjuvant Radiotherapy: What's Going On?

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ABSTRACT

Background: Treatment of breast cancer (BC) remains a constant and rapidly evolving issue for multidisciplinary breast cancer teams. Considering the emerging understanding and advances in the biological course of this disease, new trends in radiotherapy fractionation, systemic therapies, and oncoplastic surgical techniques are revolutionizing adjuvant treatment approaches to BC. Novel challenges are questioning the integration of adjuvant radiotherapy (ART) into the real-world clinical setting.

Methods: PubMed literature search was conducted in order to extract data supporting the role of new trends in breast cancer adjuvant approach according to rising issues in the multidisciplinary team discussion such as sequencing with chemotherapy (CT) plus whole breast hypofractionated radiotherapy (HF-WBRT); the role of ART after neoadjuvant CT (NACT) followed by breast conservative surgery (BCS) in early BC achieving pathological complete remission (pCR); and the integration of ART in immediate autologous breast oncoplastic reconstruction after mastectomy (a-IBR). Furthermore, there are still several concerns about toxicity with adjuvant trastuzumab emtansine (T-DM1) or breast re-irradiation after BCS relapse in long-term survivors refusing mastectomy.

Results: Among 40 hits, only 12 studies answered these issues. Many of them were retrospective studies. Less than 500 patients met the criteria for these issues and several conclusions were found exhaustive.

Conclusion: Few issues seem to have a literature solution, while there are still open questions in regard to these new trends. Novel strategies through prospective or randomized studies and new consensus guidelines are required.

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INTRODUCTION

The diagnosis of breast cancer (BC) is most common in women, with approximately 15% estimated to develop this cancer during their lifetime. Its management is a major concern because it is in constant evolution, becoming a widely discussed issue among oncoplastic surgeons, radiation oncologists, and medical oncologists.

Regarding adjuvant radiotherapy (ART), a milestone has been reached with the results of the DBCG 82bc trial,[1] which has definitely demonstrated the superior benefits of Postmastectomy Radiation Therapy (PMRT) in the long term at 30 years, disavowing the conclusions of Cuzick's meta-analysis.[2] Looking ahead, what else is going on?

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In recent decades, many novel strategies investigated in randomized trials have been introduced for the treatment of BC and are currently included in daily clinical practice.[3] With respect to ART, shorter courses of hypofractionated whole breast irradiation (HF-WBRT) consisting of 15 or 5 fractions have been advocated, as defined by large multicenter randomized trials.[4,5,6] Furthermore, novel systemic therapies have revolutionized survival advantages, and include neoadjuvant and adjuvant strategies mainly in triple-negative BC (TBNC) and HER2-non luminal BC,[7] or among HER2-positive BC patients who did not obtain a complete pathological response following neoadjuvant CT (NACT).[8]

In addition, new challenges come from oncoplastic surgery, as novel approaches with autologous immediate post-mastectomy breast reconstruction (a-IBR) question the integration of ART.[9] Although BC mortality has been reduced due to tailor-made adjuvant therapies, local recurrence rates at 10 and 15 years are still too high, ranging from 10%-20%, respectively, and 30%-40% depending on factors such as treatment, patient age, and primary tumor size.[10,11] Thus, BC-specific survival has improved, although it is reasonable to consider the risk of ipsilateral breast tumor recurrence (IBTR).[12] Unfortunately, local recurrence of BC subsequent to ART represents another therapeutic concern because salvage mastectomy is the only option. This is the standard treatment for these patients, but it could negatively impact cosmetics, quality of life (QoL), and psychological outcomes.[13,14] Perhaps, conservative treatment should be offered. In this case, breast repeated irradiation (reRT) should be considered. In fact, reRT for recurrent breast cancer is not a routine practice because of the risk of significant toxicity with reRT has minimized its widespread use, so mastectomy is the only suggested option. Given this background, in this review we aimed to find out a literature feedback to support the real-world radiation oncologist practice according to these new ongoing trends.

METHODS

A PubMed literature search was performed in September 2022 for all available articles of the last 5 years using the search terms: (“Breast Cancer Adjuvant ”) AND (“Oncoplastic Surgery OR Neoadjuvant Chemotherapy OR Hypofractionated Radiotherapy OR TDM1) AND (repeated irradiation OR omitting radiotherapy ”). All studies concerning these novel issues were included like randomized trials, systematic reviews, retrospectives studies, prospective multicenter cohort studies, and guidelines. Excluded were case reports, comments, editorials, and letters to the editor.

Data Extraction

Data extraction was performed independently by two authors (APS and IB). Discrepancies were resolved by discussion. With the extracted data, an attempt was made to answer the following research questions:

1. Adjuvant chemotherapy and hypofractionated radiotherapy: should sequencing be reconsidered?
2. NACT in patients with high-risk early breast cancer in pathological complete remission: Should we irradiate them?
3. Concurrent adjuvant radiation therapy and trastuzumab emtansine: What toxicity should be considered?
4. Autologous immediate post-mastectomy breast reconstruction: What target should be irradiated?
5. Breast reirradiation or salvage mastectomy: Is it time to break off an ancient taboo?

Outcomes

With respect to the aim of this review, data on local relapse, disease-free survival and overall survival, QoL, were extracted. For studies investigating repeat breast irradiation and new drugs combinations, data on acute, late toxicities and cosmetic outcome were collected.

RESULTS

Search

The Pub Med search yielded 40 hits; after removal of duplicates and screening the records, only 12 studies were found answering these questions analyzing less than 1000 patients treated within the last 5 years and corresponding to these issues. No studies have assessed the effect of a new sequencing with chemotherapy and hypofractionated radiotherapy, while only one retrospective cohort study met the omission of RT in pCR after NACT in early breast cancer. Only a single center preliminary study on 14 patients has evaluated the safety of the concomitant use of RT and T-DM1. Concerning the oncoplastic surgery combination with RT, only a pilot study has been conducted on 12 patients showing irrelevant results. The breast repeated irradiation yielded more data collected by 9 studies including at least 500 patients most of them treated with partial breast reirradiation.

DISCUSSION

In regard to these questions, our research has yielded some answers as follows.

Adjuvant chemotherapy and hypofractionated radiotherapy: Should sequencing be reconsidered?

Large, randomized trials with long-term follow-up have clearly shown that HF-WBRT achieves similar local control and toxicity rates compared to conventional fractionation (CF).[4,5,6] Thus, HF-WBRT has become a new standard of care after breast conservative surgery (BCS) or mastectomy around the world.[15] As a consequence, treatment exposure has been further reduced from 15 fractions to 5 fractions without any differences in long-term local control and overall survival.[16] In the meantime, schedules of adjuvant CT have been lengthened based on hormone receptor status, Her2 expression[17] and Oncotype® [18] or Endopredict®[19] profiling, which require longer times to achieve a response, and thus lead to an overextension of the start of radiotherapy (RT). In daily clinical practice, adjuvant CT always precedes RT. This sequencing was defined approximately 30 years ago based on the randomized 'Upfront-Outback' trial.[20] This historical trial randomized 244 patients to receive a 12-week CT course before or after RT after BCS. As a result, OS was 73% and 81% (P=0.11), respectively. The 5-year crude rates of first recurrence according to the site in the RT-first and CT-first groups, respectively, were 5% and 14% for local recurrence and 32% and 20% for distant or regional recurrence or both (P=0.07). The update of this study by Bellon *et al*., with a mean follow-up time of 135 months, did not show significant differences between the CT first and RT first arms in time to any event (distant metastasis), or death (P=0.88).[21] The sites of first failure and OS were also not significantly different (P=0.70 and 0.41, respectively). Although no significant advantages were found for either sequence, CT has been chosen to be administered prior to RT. Now, is there an advantage to proposing HF-WBRT? It is acknowledged that hypofractionation enhances an antitumor immune response with distant effects, and this could be true in this context. To this end, confirmation comes from a study comparing the functional and proteomic characteristics of fluid obtained from post-excisional cavities of BC patients treated with and without intraoperative radiation therapy (IORT).[22] The fluid from wound drainage of patients treated without IORT, when cocultured with breast cancer cell lines, stimulated proliferation, migration, and invasion. This effect was not observed in the wound drainage from patients in the IORT group. Proteomic analysis showed a different panel of cytokine expression in wound drainage of irradiated versus nonirradiated patients. The authors hypothesized that IORT could have had additional unknown radiobiological and immunological effects after the formation of a surgical wound. It is thus reasonable to reconsider sequencing with HF-WBRT: the time factor and immunological effect of hypofractionated radiation therapy should be considered as a rationale.[23]

NACT in patients with high-risk early breast cancer in pathological complete remission: should we irradiate them?

The use of NACT is supported by several theories based on the effect of surgery on the spread of occult disease due to the loss of tumor cells during surgery.[24] Furthermore, NACT could be considered as an in vivo test of tumor chemosensitivity that is useful in the choice of the most effective drug.[25, 26]

NACT administration in lieu of adjuvant CT in early BC is considered a novel strategy for patients with high-risk early BC cancer to achieve pCR and this effect appears to be related to improved survival.[27] In fact, the well-known pooled CT-Neo-BC analysis recorded an improvement in event-free survival (EFS) and OS in ypT0/Tis ypN0 pCR cases (hazard ratio [HR] 0.48 and 0.36, respectively) with a strong benefit in triple negative BC patients (TNBC) (EFS: HR 0.24, OS: HR 0.16) and HER2-nonluminal patients who had first received trastuzumab (EFS: HR 0.15, OS: HR 0.08).[28] Subsequently, other trials have also confirmed the positive effects on survival in this group compared to those with residual disease.[29]

Given this evidence, the integration of ART after BCS in this setting is called into question. McGuire *et al*. reported no advantages with postmastectomy ART in terms of OS and local control in patients with early BC achieving pCR.NSABP B-51[31] and Alliance A011202 trials [32] are still investigating the role of ART in the outcome of pathological nodal status after NACT. The omission of ART in patients with pCR after NACT and BCS has not yet been questioned.

The question is why we should irradiate a suspected microscopic or occult disease when the macroscopic disease has disappeared after NACT. However, interesting findings from a retrospective study conducted on a cohort of patients from the National Cancer Database (NCDB) seem to address this issue. Data from more than 5000 women from the National Cancer Database treated with NAC and BCS, who obtained a pCR, have been analyzed. Among them, 364 (7%) omitted RT and this choice was observed in women over 70 years of age, of Hispanic origin, living more than 20 miles from a treatment source, and with grade 1 disease. Interestingly, the 5-year OS rate was 94.1% with RT, 93% without RT (P=0.1783). The multivariate analysis confirmed this outcome (P=0.3181).[33] Although this study identified a subset of patients eligible for a further prospective study, in the absence of evidence of level I in the selected population, we

will continue to irradiate patients with pCR after NACT and BCS. Therefore, prospective studies are needed.

Concurrent adjuvant radiation therapy and trastuzumab emtansine: what toxicity should be considered?

The phase III KATHERINE study comparing the effects of adjuvant therapy using trastuzumab versus trastuzumab emtansine (T-DM1) on HER2-positive BC with residual invasive disease after NACT plus trastuzumab has revolutionized survival for this population.[34] In fact, adjuvant T-DM1 reduced the risk of recurrence or death by 50% versus trastuzumab ($P < 0.0001$). Thus, T-DM1 is now provided in the adjuvant treatment of patients with HER2-positive BC who achieve incomplete pathological response after treatment based on taxane and trastuzumab.[35]

Treatment is administered for 14 weeks every 21 days and usually several cycles coincide with the start of the ART course. In this case, a major concern is pulmonary toxicity, which could increase in the case of volumes irradiated with IMRT or VMAT. In the KATHERINE study, more than 80% of the treated patients received standard ART according to stage and institutional standards, and a higher incidence of pneumonitis was recorded in the T-DM1 arm than in the trastuzumab arm (3.4% vs 1.0%). The rates differed by radiation dose and fractionation schedule, radiation techniques, and prior exposure to other cancer therapies. Apart from these data, no other information is available. In this regard, a study conducted by Zolcsák *et al*. in 14 patients has evaluated the safety of this combination.[36] Ten patients received RT in the nodal areas. Pulmonary toxicity was not observed, while the most recorded side effect was grade 1 radiodermatitis and a reduced grade 2 left ventricular ejection fraction was observed in 2 patients. Therefore, the few available data suggest that acute toxicity is acceptable. Until proven otherwise, concomitant adjuvant radiation therapy T-DM1 can be administered safely without acute lung side effects. However, more detailed examination and prospective data is needed.

Autologous immediate post-mastectomy breast reconstruction: what target should be irradiated?

Oncoplastic surgery with breast reconstruction after mastectomy has improved over the last decade, with autologous immediate breast reconstruction (a-IBR) as a new surgical trend.[9] This approach raises doubts about the integration of PMRT due to a fear of a higher frequency of surgical complications. This is still a debated issue.

Previous experience has indicated that PMRT can increase the rate of complications after autologous reconstruction by approximately two to threefold.[37] In the report of Spear *et al*. on 150 TRAM flaps, despite the total complication rate being 49.5%, PMRT was associated with the worst cosmetic outcome.[38] In a study by Christante *et al*, [39] PMRT increased complications three times ($P = 0.001$) in the case of immediate breast reconstruction ($P = 0.001$), over mastectomy alone. For patients who received a combined implant plus autologous reconstruction, the complication effect, such as implant removal rate, was 31% vs 6% for patients radiated vs not radiated ($P=0.005$).

In a prospective multicenter cohort study of women diagnosed with BC in 11 centers between 2012 and 2015,[40] among the irradiated patients, autologous reconstruction was associated with a lower risk of complications than implant-based reconstruction at two years ($P = 0.007$); no differences between procedures were found in unirradiated patients. Technical issues and contour delineation in implant immediate breast reconstruction (i-IBR) have been well established.[41] The clinical target volume (CTV) of the chest in the ESTRO-ACROP guidelines consider the pathway of subcutaneous lymphatic drainage, which is critical when the skin is involved, as occurs in T4b-c-d BC. In fact, lymphatics from the mammary region drain through the dermal plexus located within the subcutaneous tissues of the breast. Considering the fact that approximately 5% to 10% of glandular tissue is retained after conventional total mastectomy as a consequence after mastectomy, the CTV of the chest wall should include residual subcutaneous glandular tissue and subcutaneous lymphatics as defined by the ESTRO guidelines. But these guidelines are not applicable in the case of oncoplastic surgery, including radical mastectomies with simultaneous breast reconstruction using the TRAM flap due to the absence of CTV in the chest. A new trend is the omission of PMRT after NACT only in patients with inflammatory breast cancer treated using this new surgical approach.[42]

This complex approach is under investigation and is offered in cases of response to NACT in scenarios with the disappearance of widespread edema of the breast skin (>30%), satellites on the breast skin, metastases in the parasternal or supraclavicular lymph nodes, upper extremity edema, complete regression (CR) or partial regression (PR) on mammography or breast magnetic resonance imaging. According to this protocol, following a radical mastectomy in Madden's modification with resection of R0, a TRAM grafting with a leg TRAM flap or a thoracodorsal flap is applied, while PMRT is not provided. In a pilot study, 12 patients with stage IIIB and IIIC breast cancer were enrolled. [42] Almost all of them had received a radical mastectomy with one-

stage reconstruction using a TRAM flap after NACT. None received RT. Two years later, one patient (8.3%) showed progression of the disease in the form of distant metastases in the bones of the spine and a patient (8.3%) had a regional relapse that occurred in the displaced flap near the postoperative scar. According to the ESTRO-ACROP guidelines,[41] complete inclusion of the pectoral chest wall under implant positioning is strongly recommended in the presence of large primary BC (pT3) treated with mastectomy and i-IBR, locally advanced BC with complete nonpathological response to primary systemic therapy, and in invasion of the main pectoral muscle and/or the chest wall.

But with the approach described above, there is no residual CTV, so is it reasonable to wonder which target should be irradiated: the scar or the regional nodal areas? On the other hand, in the ESTRO-ACROP consensus, transplanted tissues such as the skin, fat, muscles, and synthetic materials (implant, tissue expander, ADM) are not included in the calculation of the CTV. Therefore, new consensus guidelines for a-IBR are required. In the absence of level I evidence, this procedure reassesses the role of PMRT, and recommends novel consensus guidelines and a strong evidence-based multidisciplinary team consultation.

Breast repeated irradiation (reRT) or salvage mastectomy: is it time to break off an ancient taboo?

ReRT is a hot topic. Local relapse after BCS and ART has been reported in approximately 6–10% of patients at 5 years depending on the nodal status.[43] Salvage mastectomy is usually applied with or without post-operative reRT which could achieve a local control of 68–98%.[44] Alternative approaches to ensure repeat breast conservation therapy or available techniques are still under investigation. However, reRT may be effective and the trend is in favor of its use, as confirmed by a systematic review. In this analysis, among 34 eligible studies, only 18 focused on repeated BCS followed by re-irradiation (whole-breast or partial) and one on quality of life. The 5-year local control was 76% for repeat BCS alone and 89% for repeat BCS followed by reRT while the 5-year overall survival for repeat BCS and repeat BCS followed by reirradiation were 77% and 87%, respectively. [45] Furthermore, toxicity was acceptable with grade III-IV toxicity rates at least 21%, a good to excellent cosmesis in 29–100% and unacceptable in 0–18%. Thus, a reRT after BCS could be provided, and this approach seems to garner positive approval. In fact, a recent Dutch breast surgeons and radiation oncologists online survey assessed this issue, with a positive consent on reRT being collected. Almost all respondents found that a repeated conservative approach feasible in selected cases, taking into account the patient's preference and preferably with a partial breast re-irradiation modality.[46] Thus, which re-irradiation modality could be better and safer: partial breast or complete breast re-irradiation?

Partial breast reRT?

Depending on breast size, tumor dimension, molecular phenotype, focality of relapse, and availability of technology, partial breast reRT could be offered with brachytherapy, IORT, external beam radiation therapy (EBRT), and protons to achieve the best cosmetic outcome for the same local control. Interstitial multicatheter brachytherapy (MCB) has been one of the first procedures to evaluate the role of partial breast reRT (PBrI). HDR-MCB is the standard approach that delivers a dose of 34 Gy in 10 fractions, 2 fractions per day, with a minimal interval of 6 hours.[47]

In terms of efficacy and safety, according to the Balestra study, conducted on 217 patients, the 5-year recurrence rate was only 5.6% with limited grade 3-4 complications (11%).

Thus, given these results in terms of toxicity, low recurrence rate, and acceptable cosmetic results, HDR-MCB should be considered a suitable option for PBrI.[48] An alternative approach is IORT with electrons or photons. According to available studies, a single electron shot with a median dose of 20 Gy (17–21 Gy) appears to ensure a control rate of 89–95 months with a mean follow-up of 58-48 months, showing a very low acute and late toxicity profile.[49] Furthermore, in the study by Blandino *et al*, in 30 patients treated with a median dose of 18 Gy electrons, the good to excellent cosmetic outcome rate was 51%; however, G3 late fibrosis consisted of 21%.[50] Among photon studies, the most powered study by Tangarajah *et al*. involved 40 patients treated with a median dose of 20 Gy and 50kV X-rays, no grade 3-4 acute toxicity was recorded.[51] However, a PBrI with EBRT must be considered due to its widespread accessibility in all RT centers. Protocols have been provided that deliver doses ranging from 45 Gy with standard fractionation,[52] or 1.5 Gy twice daily in 15 fractions on the surgical bed.[53] To this end, the NRG Oncology/RTOG 1014 Phase 2 Clinical Trial evaluated this fractionation protocol and achieved a cumulative 5-year incidence of mastectomy of almost 10%. Continuous survival without metastases and OS at 5 years were 95% while no grade 4 or 5 toxicities were reported. Changes in breast skin and fibrosis were found to be the most common late side effects.[54] Due to their ballistic properties, proton beam PBrI could be more advantageous, but it is still under investigation with few data and short follow-up terms. The study by Thorpe *et al*. evaluating the Prospective Proton

Collaborative Group (PCG) registry, including 50 eligible patients, reported local relapse-free survival and OS at 1 year of 93% and 97%, respectively. Factors related to grade 3 toxicity were BMI > 30, bilateral disease, and IMN reRT. The median cumulative dose was > 110 Gy; however, the toxicity rate was acceptable. [55]

Whole breast reRT?

Concerning adjuvant whole breast re-irradiation (WBrI), few studies have shown how this approach is feasible with acceptable toxicities. Data on the whole breast, chest wall, and nodal areas have been reported by several retrospective studies. In the study by Merino *et al.*, 56 patients received a second course of RT with 3D conformal RT and conventional fractionation. Considering α/β ratio 3, the mean cumulative equivalent dose of 2 Gy (EQD2) to the entire breast and tumor cavity was 99.8 Gy and 109.1 Gy, respectively. The local control was 0.62 (P = 0.07) and 0.5 (P = 0.08) at 1 and 2 years, respectively. Acute toxicity was radiation dermatitis G1-2, G3, and G4 in 45, 4 and 1 cases, respectively. One patient presented necrosis. The most common late tissue toxicity was G3 fibrosis and changes in telangiectasias. By multivariate analysis, the predicative factors for local recurrence <2 years were skin involvement (P = 0.016) and the time to local recurrence (P = 0.042).[56] In the retrospective study by Fattahi *et al.*, 72 patients received reRT to the whole breast, chest wall, and nodal areas with photons, electrons, and protons with intensity modulated therapy. Grade 3 adverse events occurred in 13% of patients, indicating the time between RT courses and reRT fields as prognostic factors for grade 3 toxicity at any time. At 2 years, locoregional recurrence-free survival was 74.6% and OS was 65.5% among all patients.[57] WBrI after repeat BCS appears to be a feasible and effective option to mastectomy in the case of IBTR, but in selected patients. Factors to consider are the equivalent dose in 2 Gy for each course using an α/β ratio of 3, using a conventional fractionation, not exceeding a cumulative dose of 110–110 Gy, time factor over 2 years from first treatment and skin involvement.

Given this background, breast reRT should not be excluded and should be offered to patients refusing mastectomy, in accordance with patient factors, considering time from prior irradiation, radiation cumulative dose, and resource availability.

CONCLUSION

The growing challenges of modern advances in breast cancer oncology continue to make researchers reassess the role of ART and its relationship with surgery and systemic therapies. It is a fact that modern breast cancer adjuvant therapy has changed with these fascinating trends in an attempt to improve QoL and compliance with treatment. This review confirms that there are still open questions due to lack of a substantial level I evidence supporting the role of ART and these new ongoing trends. However, it can inform practice because some issues have yielded encouraging feedback like its relationship with novel drugs or in partial breast reRT. Questions on sequencing CT and HF-WBRT or omitting RT in pCR after NACT probably need prospective or randomized studies. ART in wide demolitive oncoplastic surgery requires substantial data and new consensus guidelines for a reconstructed CTV chest delineation. Thus, the best solution should be discussed and shared in a multidisciplinary breast cancer team, taking into account the support of the available literature.

CONFLICTS OF INTERESTS

The authors declare no competing interests.

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