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LETTER TO THE EDITOR

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Neoadjuvant radiotherapy in triple-negative breast cancer: "the past should not steal the present or hide the future"

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Triple-negative breast cancer (TNBC), with its aggressive features and dismal prognoses, remains a challenge in the optimization of breast cancer (BC) management. Despite significant advances in systemic treatment during the last two decades, approximately half of patients did not achieve a pathological complete response (pCR) and are still faced with an extremely high risk of recurrence [1]. Novel approaches to overcome intrinsic resistance to therapy incorporate ablative strategies, including radiation therapy (RT), a well-established method of inducing tumor local cell death and secondary antitumor immune responses [1]. Furthermore, the development of sophisticated technologies enabling precise delivery of high RT doses to the tumor in the preoperative setting is expected to enhance the therapeutic potential in TNBC as revealed by pCR.

Soares et al. [2] recently published their real-life experience in 127 women with locally advanced TNBC who received neoadjuvant treatment. They stated that neoadjuvant radiotherapy (NART) and the absence of pCR were independent prognostic factors for relapse and 2-year disease-free survival (DFS). Such a biased statement might be misleading and should be taken into consideration with many cautions. Actually, the 16 (13%) patients who received NART were those who experienced clinically progressive disease and/or grade 3/4 adverse events, depicting a very high-risk subgroup of patients. Yet, it would be very informative to have a detailed presentation of clinicopathological characteristics of the pre- and post-neoadjuvant therapy of these patients to better figure out the true therapeutic resistance. Moreover, no information regarding the NART delivery was reported. We assumed that a normofractionated schedule to the whole breast and/or regional lymph nodes was delivered, acknowledging the absence of adjuvant RT in these patients.

NART is not a novel approach and has been under investigation in BC with encouraging evidence, as summarized in Table 1. When delivered alone, NART can contribute to a pCR rate of 10% among all patients, and of 26% in those with TNBC disease. When sensitizing NART by concomitant administration of weekly paclitaxel, a pCR was achieved in 23% of patients, reaching 54% in patients with hormonal receptor-negative BC subtype. As observed with neoadjuvant chemotherapy (NACT), a pCR obtained from concurrent paclitaxel-RT

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was also translated into superior DFS and overall survival (OS). Moreover, "rescue" chemo-RT in NACT-refractory inoperable BC allowed curative surgery in 71% of patients, in which a pCR was observed in 50% of the histological specimens. In another study, preoperative or adjuvant concurrent chemo-RT was evaluated in 644 patients with locally advanced BC [3]. The neoadjuvant treatment was correlated with better relapse-free survival (RFS) and OS, especially in patients with cT2 tumors. Breast conservation became possible in 50.8% after neoadjuvant chemo-RT with a pCR rate of 29.2% and attained 56% in cN+ patients. This raises the question of an immune-priming phase in the involved lymph nodes and whether the modulation of RT delivery or other radiosensitizers could further improve responses.

Of note, the aforementioned studies employed standard fractionation to the whole breast and/or regional lymph nodes. Despite favorable pCR rates, TNBC patients tend to be at a higher risk of relapse and worse outcomes, especially in the case of residual disease post-neoadjuvant treatment. Every effort must be examined to ameliorate these response rates. Recent technical advancements in RT delivery offer the ability to accurately localize and target the primary disease, enabling the administration of optimal RT doses required to elicit a robust antitumor immune response with the least risk of toxicity. A phase I study tested five dose levels of stereotactic body radiation therapy (SBRT) concomitant with NACT before surgery [4]. This association showed promising results in terms of pCR rate (36%), and the highest pCR rate of 67% was achieved at the level 3 dose (25.5 Gy in 3 fractions). Interestingly, localized irradiation to the intact tumor leaves the possibility of standard-of-care adjuvant RT when indicated, especially in patients with residual disease, with no additional toxicity.

The incorporation of immunotherapy agents into the preoperative setting presents unique advantages for priming antitumor immune response and potential eradication of the disseminated micrometastatic disease. The combination of an immune checkpoint inhibitor (ICI) with hypofractionated RT (8 Gy x 3 fractions) led to increased accumulation of cytosolic DNA damage, activation of cGAS/STING, and increased type I interferon signaling, necessary for CD8+ T-cell mediated antitumor immune response and regression of non-irradiated lesions, compared to high-dose RT alone [1]. Several ongoing trials are testing this ICI/RT combination to exert the so-called abscopal effect in BC.

In conclusion, the radiation oncology community is excitingly awaiting the upcoming results of ongoing trials implementing modern concepts of NART in the management of BC, particularly, in the TNBC subtype. The matter in these combined therapies is to consider the right treatment for the right patient at the right time, which probably was not achieved in the NART patients reported by Soares et al. [2]. We strongly believe that the major unfavorable prognostic factor in their cohort was the aggressive biology of the tumors treated by NART, but not the NART itself. Therefore, in terms of NART in TNBC, we must not let the past steal the present or hide the future.

Conflict of interest

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