Lattice radiotherapy in inflammatory breast cancer: report of a first case treated with curative aim

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Inflammatory breast cancer (IBC) is a rare, aggressive form of breast cancer characterized by poor prognosis. The treatment requires a multidisciplinary approach, with neoadjuvant chemotherapy, surgery, and radiation therapy (RT). Particularly, high doses of conventional RT have been historically delivered in the adjuvant setting after chemotherapy and mastectomy or as radical treatment in patients ineligible for surgery. Here, we report the case of a 49-year-old woman patient with IBC unsuitable for surgery and treated with a combination of lattice RT and fractionated external beam RT concurrent with trastuzumab, with a curative aim. One year after RT, the patient showed a complete response and tolerable toxicities. This is the first reported case of a not-operable IBC patient treated with this particular kind of RT.

Keywords: Inflammatory breast cancer, Radiation recall dermatitis, Trastuzumab, Radiation therapy, Hypofractionation

Introduction

Inflammatory breast cancer (IBC) is a rare, aggressive form of locally advanced breast cancer characterized by a poor prognosis. The main clinical features are breast erythema, edema and/or peau d'orange with or without an underlying palpable tumor [1].

Some specific biological factors, such as the presence or not of estrogen and progestin receptors and human epidermal growth factor receptor 2 (HER2/neu) overexpression define both therapeutic choice and prognosis.

According to the European Society for Medical Oncology guidelines, the treatment of IBC includes a trimodal approach with chemotherapy, hormonal therapy, and radiation therapy (RT) with or without surgery [2]. This kind of treatment demonstrated to improve both local/distant disease control and survival. Neoadjuvant chemotherapy (NAC) is the first step of this regimen; in case of a complete or near-complete local response, it will be planned a modified radical mastectomy with axillary dissection followed by chest wall plus regional nodes irradiation. In some patients with an incomplete response to NAC, the surgery could be not indicated [3].

In this instance, high doses of RT alone (up to 70 Gy or altered fractionation) represent a valid alternative to surgery with a 10-year locoregional relapse rate of 26% [4].

An emerging approach to obtain altered fractionation is lattice RT (LTRT) which can be used both in a radical setting and for the treatment of bulky tumors in stage IV. LTRT is a type of spatially fractionated RT (SFRT), in which high radiation doses are precisely delivered to different areas within the gross tumor volumes (GTV)
without exceeding the organs at risk tolerance resulting safe and well tolerated. The spatial fractionation causes the so-called “valley-to-peak dose ratio”: the ratio of the valley dose (lower doses – cold spots) and the peak doses, also called the vertex (higher doses – hot spots). Combining LTRT with external beam RT (EBRT) to all GTV optimal symptom control and clinical response were observed [5]. Radiobiological experiments support the role of radiation-induced bystander effects, vascular alterations, and immunologic interactions in areas subject to low-dose radiation [6]. The “absco-pal” and “bystander” effects respectively determine the tumors’ shrinkage at a distance from the irradiated volume and the radiation-induced damage in nearby unirradiated cells in addition to direct RT damage beyond other vascular effects, stem cell migration, and immune effect [7].

Here, we report a case of a female patient with IBC plus palpable breast cancer treated with a curative aim combining LTRT and EBRT after NAC.

Case Report

In October 2021, a 49-year-old woman showed an IBC concomitant to a nodular breast tumor diagnosed with ultrasonography and mammography exams followed by a biopsy of the primary lesion. Histological examination reported an invasive ductal carcinoma; immunohistochemically a hormone receptor (HR+), HER2/neu positivity with a Ki-67 value of 20% has been reported.

The patient underwent contrast-enhanced computed tomography (CT) of brain–chest–abdomen followed by positron emission tomography/CT (PET/CT) scan. A 18F-fluorodeoxyglucose (18F-FDG) PET uptakes revealed a primary breast tumor, involvement of locoregional lymph nodes and metastasis in a single paratracheal lymph node concomitant to symptomatic IBC (Fig. 1A). Patients had erythema, edema, nipple retraction, peau d’orange affecting a large area of the breast, and homolateral lymphedema (Fig. 2).

According to multidisciplinary disease management programs, a bio-chemotherapy based on trastuzumab–pertuzumab–docetaxel for seven cycles was administered from March to September 2022. A 18F-FDG PET/CT was performed after six cycles of systemic therapy and a complete and partial response was observed in paratracheal lymph and in locoregional nodes, respectively (Fig. 1B).

Due to the clinical and radiological persistence of IBC, patient has been considered unsuitable for mastectomy. Therefore, a radical RT was considered as an alternative non-surgical locoregional treatment [3].

1. Treatment planning and dosimetry

RT treatment provided a combined approach of therapeutic techniques; in fact, patient underwent SFRT followed, after 72 hours, by EBRT using volumetric modulated arc therapy (VMAT).

The patient was simulated in the treatment position, with both arms above the head, using appropriate immobilization (Bionix breast radiation therapy system) on the SOMATOM Sensation 16 Slice CT (Siemens Healthineers, Erlangen, Germany). Slices of 3 mm thickness were obtained from the base of the neck to the xiphisternum level. Subsequently, simulation plan data were transferred to the Monaco treatment planning system (Elekta AB, Stockholm, Sweden).

For SFRT, CT scans for planning purpose were co-registered with a post-chemotherapy 18F-FDG-PET/CT and a dose on a single sphere in a single fraction of 10 Gy was delivered.

The only nodular intraparenchymal area was considered as GTV, therefore only one sphere with a 1-cm diameter was allocated within GTV as a target region and was outlined in a transitional area at different standardized uptake value (SUV) (Fig. 3). The cut-off value of SUV was determined in our previous case series [5]. The ipsilateral breast, contralateral breast, skin, chest wall, lungs, heart, and thyroid were delineated as organs at risk (OARs).

The VMAT technique, thanks to its several degrees of freedom provide a better dose homogeneity within the target and helps in achieving dose constraints to OARs. To deliver a sufficient dose on the tumor tissue under the skin, used a surface bolus (water equivalent build-up material, 0.5 mm thickness). The target volume definition included remanent breast, skin, subcutaneous fat (IBC), and lymph node area.

Treatment plans were generated with two partial arcs and optimized with Pareto mode for X-ray photon beam of 6 MV energy of Elekta Synergy Platform linear accelerator (Elekta Medical Systems, Crawly, UK). The total prescribed dose was 60 Gy in 30 fractions on breast (clinical target volume [CTV]1), 50 Gy in 25 fractions on axillary lymph nodes (CTV2), and 46 Gy in 23 fractions on supravacuicular lymph nodes (CTV3) over a period of 6 weeks (Fig. 4). All the dosimetry analyses were based on the International Commission of Radiological Units and Measurements Reports 50 and 62. The dosimetry quantities were obtained for $V_{10}$, $V_{15}$, and $D_{max}$ for target volume, $V_{20}$, $V_{30}$, $V_{50}$ for ipsilateral lung and both lungs.

2. Clinical and radiological evolution

At the end of two therapy phases, the patient presented moderate locoregional toxicities represented by radio-dermatitis grade 3 associated with mammary edema, pain, and pruritus ≥ grade 2. This clinical condition has been treated with oral corticosteroids and topic lotions with complete resolution of symptoms and clinical objectivity in 4 weeks. Trastuzumab was given as maintenance systemic therapy; 6 weeks after the end of RT, the patient showed an
Fig. 1. (A) A 18F-fluorodeoxyglucose positron emission tomography (18F-FDG PET) uptake in the primary breast tumor, locoregional lymph nodes, and metastasis in the paratracheal lymph node before the treatment. (B) A 18F-FDG PET uptake shows partial response in locoregional lymph nodes and complete response in the paratracheal lymph node after 7 cycles of trastuzumab-pertuzumab-docetaxel. (C) A 18F-FDG PET can show a metabolic complete remission of breast solid tumor and locoregional node 6 months after radiotherapy.

Fig. 2. (A, B) Erythema, edema, nipple retraction, and peau d’orange at diagnosis.

inflammatory cutaneous reaction on the breast and ipsilateral arm that can occur as radiation recall dermatitis. The symptoms were resolved with administration of oral antihistamine and a low dose of corticosteroids for 5 days (Fig. 5). Four months after RT, a mammography and axillary ultrasound showed a complete response of breast solid tumor whereas a metabolic complete remission on 18F-FDG PET/CT was appreciable 6 months after radiotherapy.

Discussion

Using “metabolism-guided” LTRT followed by EBRT it is possible to obtain a complete remission of disease in IBC patient with residual...
disease after NAC. In fact, at 1-year follow-up, our case is disease-free in absence of late toxicities.

During RT we observed a grade 3 radiation dermatitis which is justified by the use of bolus to superficialize radiation dose delivered, avoiding the so-called build-up effect own of high-energy X-ray radiation. The use of bolus is a well-known risk factor for radiation-induced dermatitis [8].

After 6 months of RT, concomitant to maintenance trastuzumab monotherapy, we observed a radiation recall dermatitis, with an inflammatory cutaneous reaction, erythema on the breast and ipsilateral arm identical in type to RT field resolved with administration of oral antihistamine and a low dose of corticosteroids for 5 days. Shrimali et al. [9], in 2009 published the first case of the radiation recall phenomenon during the administration of trastuzumab; a recent literature revision on this issue reported eight cases until 2023. The present case is the 9th reported in English language literature. It is hard to link both acute dermatitis and radiation recall, to the use of lattice technique [10].

Our patient received combined RT with an association of VMAT and hypofractionated RT in the form of LTRT. Using the VMAT technique a total dose of 60 Gy, 50 Gy, and 46 Gy were prescribed on the wall breast, on axillar lymph nodes, and on supraclavicular lymph nodes, respectively, over a period of 6 weeks. With LTRT a single dose of 10 Gy was delivered within areas at different SUV, detected on 18F-FDG PET/CT as described in previous paper [5].

Several studies reported radiation doses of 60 Gy until 90 Gy with conventional fractionation to whole breast and doses of 50–60 Gy if the nodal area resulted negative or positive, respectively [4-11].

In 1995, Thomas et al. [12] reported a case series of patients treated with hypofractionation (2.5 Gy 4 days/week) with a 10-year local control of 74%.

LTRT is an example of altered fractionation which has experiences delivering are emerging but mostly collected in small case series. Currently, this therapeutic approach has been mainly employed and investigated for palliative purposes for the treatment of bulky tumors in metastatic patients and has been applied to heterogeneous

Fig. 3. (A) Sphere in transitional area at different standardized uptake value. (B) Treatment plan of lattice radiotherapy (dose to vertex).

Fig. 4. Volumetric modulated arc therapy treatment plan in axial (A) and coronal (B) scans.
both site and histologic diagnosis. In 2010, Amendola et al. [13] used LTRT in a large squamous cell cervical carcinoma (915 mL) homogeneously irradiated with 1.8 Gy/day fractions up to 36 Gy simultaneously to a boost of 2.4 Gy/20 fractions to a total dose of 48 Gy. This treatment obtained a complete pathological response, as documented after surgery [13]. A similar experience is reported by Ferini et al. [14] delivering LTRT in a median line relapse of locally advanced cervical carcinoma. The treatment course provided two phases: 27 Gy in 3 fractions positioning three vertices followed by 45 Gy in 25 fractions to CTV. Three months after the completion of RT, a 18F-FDG PET/CT documented a complete remission of the bulky tumor.

The LTRT technique is also implemented using 18F-FDG PET/TC in order to investigate the local distribution of oxygenated areas and define a new approach so-called “metabolism-guided RT.” In a series of 30 patients who underwent this “modify”-LTRT approach, the therapy was well tolerated, allowing to achieve very impressive results both in terms of symptom relief and overall clinical response rate in stage IV bulky disease. The treatment plan included a median total dose delivered on CTV of 20 Gy/4 fractions and 15 Gy/1 fraction on each vertex positioned between the area showing SUV > 75% SUVmax and the remaining part of the “Avid” PET area with SUV > 2.5 [5].

Recently, Pollack et al. [4] conducted a trial with the aim of demonstrating the feasibility of the combined treatment, the up-front lattice boost plus EBRT, in patients with prostate cancer patients. With a follow-up of 66 months, the association is demonstrated safe, with a biochemical failure of 8% and without toxicity. The efficacy of SFRT is also improved by the association with immunotherapy due to non-target as “abscopal” and “bystander” [6-16]. This combination was evaluated in a preclinical assessment using a mouse model with triple-negative breast cancer by Johnsrud et al. [17]. This study suggests that systemic immune activation may be triggered by SFRT to a primary lesion and promote anti-tumor immune responses outside the treatment field. Based on these results, other authors explored the use of the GammaPod-based lattice technique for treating large bulky breast tumors reporting the dosimetric feasibility. In fact, despite the high dose concentrated at vertices, a very-low mean dose to overlying skin (1–2 Gy) was obtained [18]. This evidence demonstrates that LTRT can be used to pursue a curative intent in different difficult-to-manage cases [6].

Here, we report a case of IBC treated with LTRT with a curative aim. This case highlights that the results obtained by combining high vertex RT with low doses to GTV capable of producing bystander, abscopal, and immunological effects are feasible and tolerated, with an acceptable toxicity profile. Therefore, we cannot rule out the possibility that this kind of therapy could emerge as a valid therapeutic option for these patients’ setting and further studies are necessary.
Statement of Ethics

Patients signed informed consent regarding publishing their data.

Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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Author Contributions

Conceptualization, AP, S.Pe; Methodology, S.Pa, PC; Validation, AP, GF; Formal analysis, CS, AB; Investigation, MS, VV, CN, IS; Data curation, GF, FC; Writing_original draft, S.Pa, PC; Writing_review and editing, S.Pa, PC, AP, S.Pe; Supervision, GF, S.Pe.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

References


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