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ORIGINAL RESEARCH

Ultra-Hypofractionated Whole Breast Radiotherapy with Automated Hybrid-VMAT Technique: A Pilot Study on Safety, Skin Toxicity and Aesthetic Outcomes

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Purpose: The most prevalent treatment-related side effect related to adjuvant radiotherapy (RT) for breast cancer is acute skin toxicity in the irradiated area. The purpose of this single-institution pilot study is to provide preliminary clinical results on the feasibility and safety of a breast ultra-hypofractionated radiation treatment delivered using an automated hybrid-VMAT technique. Skin damage was assessed both with clinical examination and objectively using a Cutometer equipment.

Patients and Methods: Patients received 26 Gy to the whole breast and 30 Gy to the tumoral bed in 5 fractions using an automated hybrid-VMAT approach with the option for the breath hold technique if necessary. Acute and late toxicities were clinically evaluated at baseline, 1- and 6-months after treatment using the CTC-AE v.5.0 scale. An instrumental evaluation of the skin elasticity was performed using a Cutometer® Dual MP580. Two parameters per patient, R0 (the total skin firmness) and Q1 (the elastic recovery), were registered at the different timelines.

Results: From June 2022 to January 2024, 30 patients, stage T1-T2, N0 were enrolled in the study. Four out of 30 (13.3%) patients reported G2 acute skin toxicities. At 6 months, G2 late toxicity was registered in 3 patients (10%). A total of 2160 measures of R0 and Q1 were recorded. At 1 month after treatment, no correlation was found between measured values of R0 and Q1 and clinical evaluation. At 6 months after treatment, clinical late toxicity ≥1 was strongly associated with decreased R0 and Q1 values ≥24% ($p = 0.003$) and ≥18% ($p = 0.022$), respectively.

Conclusion: Ultra-hypofractionated whole-breast radiotherapy, when supported by advanced treatment techniques, is both feasible and safe. No severe adverse effects were observed at any of the different timeframes. Acute and late skin toxicities were shown to be lower in contrast to data presented in the literature.

Keywords: breast cancer, ultra-hypofractionated radiotherapy, Cutometer, hybrid-VMAT technique

Introduction

Adjuvant radiotherapy (RT) after conservative surgery is the standard of care for early breast cancer (BC), reducing the 10-year risk of any (ie, locoregional or distant) first recurrence from 35% to 19.3% and reducing the 15-year risk of breast cancer death from 25.2% to 21.4%.[1]

Recently, data have been published on the long-term outcomes of a five-fraction schedule delivered in one week,[2] allowing simplified curative radiotherapy for women with early-stage BC malignancy. Specifically, the randomized Phase III Fast Forward trial results showed that 26 Gy in five fractions over 1 week is just as effective as the standard treatment of 40 Gy in 15 fractions over 3 weeks for local control. Additionally, the treatment was equally safe in terms of toxicity

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up to 5 years for patients who receive adjuvant local RT after primary surgery for early-stage BC.[2,3] Finally, in patients who meet the study's inclusion criteria, the one-week treatment schedule offers significant advantages over three- or five-week schedules in terms of convenience and cost for patients and healthcare services worldwide.[3,4]

Regarding the RT technique, some new techniques have been proposed in recent decades to achieve homogeneous dose distributions, aiming to reduce toxicity and improve aesthetic results. The "field-in-field" RT technique used two open tangential photon beams and a small number of subfields, whose shapes and weights were determined manually to decrease hot-spot regions within the breast volume.[5,6] This technique was time-consuming and largely operator-dependent. New techniques, such as intensity modulated radiotherapy (IMRT) and volumetric modulated arc therapy (VMAT), have enabled simultaneous integrated boost (SIB), delivering an overdose to the tumor bed concurrently with irradiation of the entire mammary gland. This approach avoids prolonging treatment time and takes advantage of the increased sensitivity of breast tumor cells to hypofractionation.[7] Compared to the sequential boost technique, SIB has demonstrated improved tumor bed dose homogeneity and decreased dose to normal tissues.[8–10] However, all of the advantages mentioned above of IMRT techniques, in terms of homogeneity and dose compliance, are achieved at the cost of increased bathing of low doses to healthy tissues, so the potential risk of developing of second tumors is not negligible.[11]

In particular, the use of the full VMAT technique for irradiation of the left breast or chest wall is not common, and the results of some dosimetric studies are contradictory.[12,13] Our center recently set up a breast ultra-hypofractionated RT implemented with an automated hybrid-VMAT technique, with recently published dosimetric results.[14,15] In the hybrid approach, conventional standard treatment and VMAT treatments are combined, aiming to generate a good balance between homogeneous dose distributions and the robustness of the treatment plan. The highest percentage of the prescribed dose (eg, 70–80%) is delivered through open tangential fields, while the remaining prescribed dose (eg, 20–30%) is delivered through one/two partial VMAT arcs. The partial arcs are then optimized by the reverse planning system to increase homogeneity to the target and dose coverage. The effectiveness of this technique has been investigated by dosimetric studies, all reporting that the hybrid technique allows for greater dose uniformity in the breast, lower irradiation of the lung, and less complex planning procedures than either totally IMRT or totally VMAT techniques.[14–17] In the last year, we transferred these promising in silico results to our clinical practice.

Radiotherapy, in the clinical counterpart, may affect the ipsilateral lung, the heart, the epidermal and subcutaneous tissues of the omo- and contralateral breasts, generating toxicities in the area where it is administered. Acute skin toxicity in the irradiated area is the most common side effect of treatment, ranging from mild redness with or without scaling to an extremely rare, severe, and painful redness with wet dermal exfoliation. Nevertheless, this phenomenon is often mild and has minimal impact on quality of life, particularly in the context of modern radiotherapy. Consequently, there is no single locally applied treatment that is widely accepted as being highly effective. Several active ingredients have been evaluated in creams and lotions for management of skin toxicity[18,19] Among hyaluronic acid-based creams, a medical device (LimpiAD 2.5% cream or foam, @Aileens Pharma s.r.l.) containing c-40 hyaluronic acid conjugate (HA c-40) has been studied in murine and human models with promising results, demonstrating the ability to lower the inflammation triggering in the treatment of inverse psoriasis, pressure ulcers, and seborrheic dermatitis.[20–22] We selected this medical device for our study due to its intriguing mechanism of action and the fact that it had never been tested in a radiotherapy setting.

Herein, we report the preliminary clinical results of a breast ultra-hypofractionated RT implemented with an automated hybrid-VMAT technique, with the option for the breath hold technique if necessary and the use of the LimpiAD medical device (@Aileens Pharma s.r.l.), administered as supportive care to prevent skin toxicity. In addition to clinical examination, an objective instrumental assessment of skin elasticity using a Cutometer device was performed.

Materials and Methods

Study Design and End-Points

This is a single-institution pilot study. The primary study endpoint was to provide preliminary clinical results on the feasibility and safety of an automated hybrid-VMAT technique. This was achieved by evaluating the acute (1 month later) and late (6 months later) toxicities at the site of irradiation, namely the skin and subcutaneous tissues of the irradiated breast, the ipsilateral lung, the contralateral breast, and the heart. The secondary end-points were the evaluation

of the correlation between subjective and objective toxicity data and the aesthetic outcomes. The trial, coordinated and performed at the Radiotherapy Unit of the Responsible Research Hospital, Campobasso, Italy, was conducted according to the guidelines established in the Declaration of Helsinki, and the protocol was approved by the Internal Responsible Research Hospital Committee. All participating patients signed an informed consent document.

Patients Selection

The study enrolled and analyzed patients who received conservative surgery (quadrantectomy, wide excision, lumpectomy) and sentinel lymph node examination and reported an invasive breast cancer diagnosis. The study required patients to meet specific criteria, including being 45 or older than 45, having a pathologic stage of pT1-3 pN0-1 M0, and having resection margins free of infiltration (at least 2mm away from the presence of neoplastic cells, except foci of LCIS and/or atypical hyperplasia). Premenopausal pT1N0s M0 patients undergoing conservative surgery with resection margins free of infiltration or neoadjuvant and/or adjuvant chemo-hormonal treatments, if needed, did not preclude the access to treatment. Exclusion criteria were <45 years of age, previous mastectomy, unknown or infiltrated resection margins or margins less than 2mm away from neoplastic cells. Additionally, patients who required nodal irradiation or had severe co-morbidities that prevented proper treatment and follow-up were excluded. Absolute contraindications for radiation treatment included pregnancy or inability to maintain the correct position. Relative contraindications for study enrollment included connective tissue diseases and patient refusal to use data for research purposes.

Radiotherapy Treatment

All patients were simulated and treated in a supine position within the C-Qual TM Breastboard system (Civco Medical Solutions, Kalona, IA, USA). Computed tomography (CT) scans (Brilliance Big Bore, Philips, UK) were performed with slice thickness acquisition of 3mm. For left-breast treatment, the deep-inspiration breath hold (DIBH) technique was used to spare the heart and ipsilateral lung, if clinically necessary.

The two clinical volumes (CTVs) included the breast (CTVB) and the tumor bed (CTVTB). In particular, the CTVTB was delineated according to preoperative and operative reports, including the surgical clips and/or any surgery-induced changes considered part of the lumpectomy cavity (hematoma or seroma). The corresponding planning volumes (PTVB and PTVTB) were generated by expanding the CTVs by 8mm, restricted by 5mm from the external body. The normal organs at risk (OaR) included the heart, the ipsilateral lung, and the contralateral breast. The automated hybrid-VMAT (HVMAT) plans were generated using the Pinnacle TPS v.16.2 (Philips Healthcare, Fitchburg, WI, USA). The collapsed cone algorithm was used for dose calculations with a dose calculation grid of 2mm.[23] Prescribed doses were 26 Gy to the residual mammary gland (PTVB) in 5.2 Gy per fraction and a simultaneous integrated boost of 6 Gy per fraction to the tumor bed (PTVTB). The treatment plans were optimized according to Fast Forward Protocol.[2,3] In particular, >95% PTVs received 95%, ≤5% PTVs received 105%, ≤2% PTVs received 107% of the prescribed dose (PD). The maximum dose to PTVs had to be ≤107% of the PD. Moreover, the dose constraints for heart volume were <25%, and <5% had to receive 5% and 25% of the PD, respectively. When feasible, the mean dose to the heart was reduced to less than 3 Gy, but it was never allowed to exceed 4 Gy.

Concerning the ipsilateral lung, <15% had to receive 30% of the PD. Finally, volume of contralateral breast receiving 5 Gy had to be less than 1 cc as well as less than 15% of the PD.

The HVMAT technique has already been described.[23] RT was performed daily for 5 days using a Linear Accelerator with a 6 MV photon regimen. The medical device LimpiAD (@Aileens Pharma s.r.l). (2.5% cream or foam) containing HA c-40 was applied twice a day during treatment and for 2 weeks after to protect the skin and prevent subcutaneous radio-induced toxicity.

Clinical Assessment of Toxicity

The clinical evaluation was performed before the start of radiation therapy (RT), at the end of treatment, and at 2 weeks, 1 month, 6 months, and every 12 months thereafter. At each follow-up visit, all acute and late toxicities were assessed according to CTCAE (Common Terminology Criteria for Adverse Events) v5.0 scale.[24] The aesthetic evaluation was graded by the physician and by the patient at different time points, and the results were classified according to the

Harvard scale.[25] Photographic documentation before and after treatment was performed.[26] For the evaluation of Quality of Life, the EORTC (European Organization for Research and Treatment of Cancer) QLQ-C30 and EORTC-QLQ-BR23 questionnaires[27,28] were administered at different time points. Oncologic follow-up was performed according to the center's policy.

Instrumental Assessment of Toxicity

An additional objective assessment of the skin and subcutaneous tissues was planned to determine the percentage of firmness and elastic recovery loss owing to treatment at baseline, one month, six months, and one, two, and five years after treatment completion. This examination was carried out by comparing the treated and untreated mammary glands in four different regions. Cutometer® Dual MP580 (G.F. Secchi, Erba, CO, Italy) was the equipment used to objectively/instrumentally measure skin firmness and elastic recovery over many timeframes with no inter-observer variability. Cutometer is a non-invasive device instrument that detects skin elasticity parameters based on the suction method through a probe that applies negative pressure to the skin followed by a release. The instrument software analyzes the curve resulting from the probe and processes numerical parameters, providing different skin distensibility and elasticity indices, including R0, ie, the total skin firmness measured in millimeters and Q1, ie, the elastic recovery measured as a percentage.[29,30] A well-trained investigator (MaF) performed all measurements in a temperature-controlled environment (23 °C); all patients remained supine for 15 min before the measurements.

Statistical Analysis

The categorical data were reported with frequencies and percentages, and continuous data were reported with median and range. The Mann–Whitney *U*-test was employed to evaluate the correlation between the ≥ G1 clinical late toxicity and the R0 and Q1 values. Statistical significance was set for p-values of 0.05 or lower. Statistical analysis was performed using the XLSTAT statistical packages (Addinsoft, New York, NY, USA).

Results

A total of 30 patients, with a median age of 67 (45–86) years, were enrolled in this pilot study between July 2022 and January 2024 and completed adjuvant radiotherapy. All patients were stage T1-T2, N0, with two-thirds having G2 grading (63.3%). Fifteen (50%) patients had hypertension, and 3 (10%) patients had diabetes. About half of the patients were overweight or obese, according to body mass index (BMI). Most patients (96.7%) were on hormone therapy maintenance (Table 1). From a dosimetric point of view, all radiotherapic plans satisfied the desired coverage of the PTVs and OaR constraints.

According to the study's primary endpoint, the automated hybrid VMAT technique was safe, with no serious toxicities (grade ≥ 3) reported in the irradiated area and involved OARs (Table 2). Twenty-five patients (83.3%) experienced mild acute toxicity at one-month follow-up; the majority (63.3%) were hyperchromia and erythema Grade 1. Only 4 (13.3%) G2 acute skin toxicity were reported divided as follows: 2 erythemas, one oedema, and one epitheliolysis. Furthermore, only 6 (20%) patients experienced low-grade breast pain at the one-month follow-up.

Nineteen (63.3%) patients presented late toxicities: 3 (10%) grade 2 skin indurations and 19 (63.3%) hyperchromia and induration G1 (Table 2). No lung or heart or contralateral breast toxicities were observed.

As per the instrumental evaluation of epidermal and subcutaneous tissues of the omo- and contralateral breasts, a total of 2160 measures of two parameters, R0 (the total skin firmness, mm) and Q1 (the elastic recovery, %), were recorded using the Cutometer® Dual MP580. The device was able to detect small variations in skin elasticity following RT. One month following the treatment, no correlation was identified between the measured values of R0 and Q1 and the clinical evaluation. Six months after the RT treatment, a reduction of R0 values ≥24% was strongly correlated with clinical late toxicity Grade ≥1 ($p = 0.003$). Similarly, a decrease of Q1 values ≥18% was correlated with clinical late toxicity Grade ≥1 ($p = 0.022$) (Figure 1). Smaller decreases of R0 and Q1 were not clinically detected.

All patients used LimpiAD (@Aileens Pharma s.r.l.) medical device during and after treatment with an optimal cream/foam compliance. The physician and patient completed an aesthetic assessment using the Harvard scale[25] before and 6 months after RT (Table 3). Aesthetic outcomes graded as "good" or "excellent" were self-reported by 25 patients at

Table 1 Patients' Characteristics (30 Patients)

	N (%)
Median age, range	67, 45–86
BMI	
Underweight (<18.5) Healthy Weight (18.5–24.9) Overweight (25–29.9) Obesity (≥30)	1 (3.3) 13 (43.3) 8 (26.7) 8 (26.7)
Comorbidities	
Yes — Hypertension — Diabetes No	18 (60) 15 (50) 3 (10) 12 (40)
Other treatments	
Hormonal Therapy Neoadjuvant chemotherapy Neoadjuvant Anti Her2 therapy Adjuvant chemotherapy Adjuvant Anti Her2 therapy	29 (96.7) 1 (3.3) 1 (3.3) 2 (6.7) 1 (3.3)
Staging	
pT1 N0 pT2 N0	27 (90) 3 (10)
Grading	
G1 G2 G3	8 (26.7) 19 (63.3) 3 (10)

Abbreviation: BMI, Body Mass Index.

Table 2 Acute and Late Skin Toxicity

Acute toxicity	**G1**	**G2**
	N (%)	**N (%)**
Skin hyperchromia	12 (40)	–
Skin erythema	7 (23.3)	2 (6.7)
Skin itch	6 (20)	–
Skin edema	4 (13.3)	1 (3.3)
Epitheliolysis	1 (3.3)	1 (3.3)
Dry skin	1 (3.3)	–
Skin ulceration	1 (3.3)	–
Late toxicity		
Skin hyperchromia	9 (30)	–
Skin induration	10 (33.3)	3 (10)
Fat atrophy	1 (3.3)	–
Dry skin	1 (3.3)	–

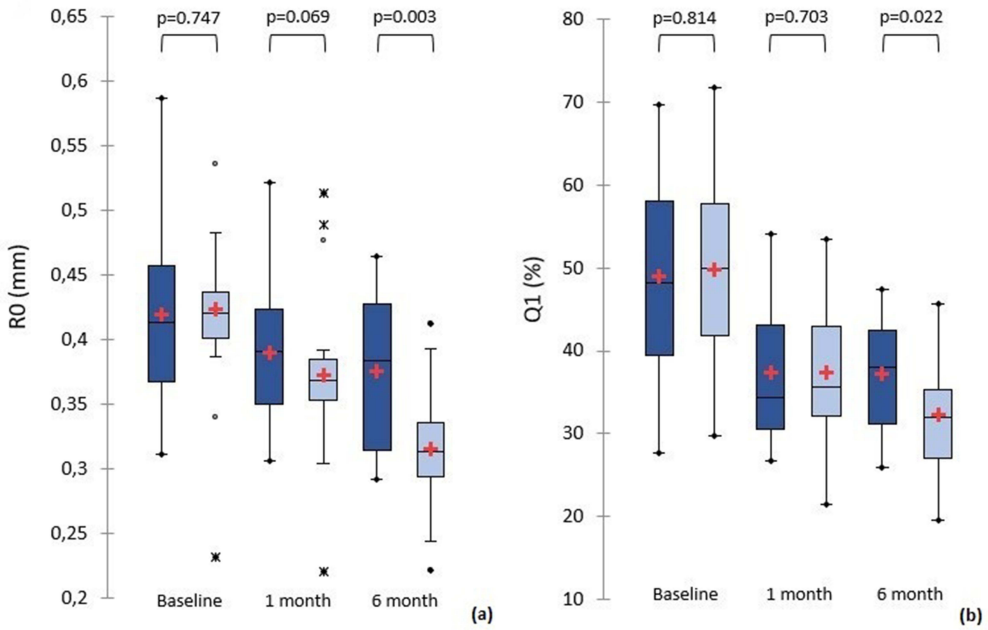

Figure 1 Box-and-whisker plots for (**a**) R0 and (**b**) Q1 values at baseline, one-month, and six-month intervals in patients without (dark blue boxes) or with ≥G1 clinical late toxicity (light blue boxes). The median is indicated by the central horizontal line; the 25th and 75th percentiles are indicated by the box's edges; the outlier's values are represented by black circles and crosses; the mean values are indicated by red crosses.

baseline and 29 at 6 months after RT. The same evaluation was made by the radiation oncologists: a "good" or "excellent" judgment was expressed in 25 and in 27 patients at baseline and at 6 months follow-up, respectively. Due to the study's short follow-up, no data on quality of life have been reported.

Discussion

In this pilot study, 30 breast cancer patients were postoperatively treated with breast ultra-hypofractionated radiotherapy, implemented with an automated hybrid-VMAT technique. The adoption of the deep inspiration breath hold technique for left-breast treatment, as well as a medical device as supportive care to prevent skin toxicity, were technical/clinical corollaries that helped to optimize the treatment. The treatment was well tolerated, indeed, as per the primary end-point, we registered very acceptable acute and late toxicity rates, with no patients suffering from any severe adverse effects. No ipsilateral lung or heart or contralateral breast toxicities were observed at the different timeframes.

As expected, the more represented were acute and late skin toxicities, all of them mild or moderate. In comparison with available literature, the Fast Forward protocol[3] accounted for acute and late Grade 2 skin toxicity incidences of 36% and 11.9%, respectively. Our results reported 13.3% and 10.0% of acute and late Grade 2 skin toxicities and should be considered really encouraging, probably favored by the advanced treatment delivery techniques. Although there are currently no official guidelines for preventing or reducing skin toxicity,[31] this pilot study utilized all available methods to minimize all potential toxicity. Firstly, all patients received advanced radiation therapy techniques and were treated with deep inspiration breath

Table 3 Aesthetics Assessment

	Baseline		6 Months Follow-Up	
	Patient (n)	**Radiation Oncologist (n)**	**Patient (n)**	**Radiation Oncologist (n)**
Excellent	6	4	6	10
Good	19	21	23	17
Fair	5	5	2	2

hold for left breast irradiation.[32] Then, planning automation was used in the treatment planning phase based on a previous study identifying automation as the best-in-class solution for breast cancer.[15] Additionally, patients applied a medical device containing HA c-40 during and 2 weeks after radiation therapy to relieve and control skin irritation. Indeed, the reduction of skin toxicity has been mainly achieved through highly conformal techniques and automation treatment planning, but we cannot exclude that a further contribution was given by the choice of LimpiAD medical device whose patented component, HA c-40, creates an invisible, non-occlusive protective layer that shields and defends against external factors, reduces fluid loss, and keeps the skin moisturized. Previous studies have shown that it also prevents the adhesion of microbes, counteracts dysbiosis, and binds and sequesters microbial catabolites, thereby reducing inflammation-inducing stimuli and hindering the mechanisms underlying inflammatory processes.[33,34] Further studies with a larger sample size are needed to compare the skin toxicity results of patients who did or did not use the LimpiAD medical device.

The study included, as secondary endpoint, the evaluation of the correlation between subjective (clinical) and objective (instrumental) toxicity data. An added value in the accomplishment of this analysis was due to a device, the Cutometer® Dual MP580, firstly reported in this treatment setting, that allowed the objective assessment of skin firmness and elastic recovery. The device allows for standardized quantitative assessment of elastic-viscosimetric skin characteristics and their reduction with treatment. It was previously used to evaluate epidermal hydration[29] and skin elasticity.[35] The device was able to detect small changes in skin elasticity after RT and allow us to find a correlation between clinical late toxicity Grade ≥1 and specific Cutometer parameters. A reduction in R0 and Q1 Cutometer values below a defined threshold was found to be associated with the occurrence of clinical toxicity six months after treatment. If validated by other researchers, the Cutometer parameters could serve as objective and quantitative markers of skin elasticity, thereby providing a tool to identify and prevent more serious toxicity following radiotherapy. Of course, these results could be extended to several tumors and treatments, eg, head and neck, where skin toxicity represents a major issue.

Finally, the study confirmed that the ultra-hypofractionated schedule does not affect the aesthetic outcomes. The baseline and 6-months aesthetic evaluations by patients and radiation oncologists, according to the Harvard scale,[25] were comparable. The evaluations showed that the treatment did not worsen patient's aesthetics. In contrast, both patients and physicians observed an improvement in the aesthetic appearance of the surgical site as time elapsed since the procedure.

A critical examination of the strengths and weaknesses of the paper reveals that this study enrolled a limited number of patients, which constrains the scope for drawing any meaningful conclusions. Therefore, the study is only able to facilitate a comparison of the raw acute and late toxicity rates with those observed in historical data. Moreover, a comparison of the technique's results with existing literature is not possible due to the recent implementation of this innovative technique. Furthermore, the utilization of a medical device to mitigate cutaneous toxicity may introduce a potential source of bias, underscoring the necessity for further investigation in this domain.

However, this trial is unique because it combines several approaches (robust high-modulated delivery techniques, state-of-the-art automated planning, deep inspiration breath hold) with the aim to reduce all types of toxicities and improve dose homogeneity. In addition, the skin clinical toxicities evaluation was correlated to the instrumental measurements performed by the same operator (MaF) using the Cutometer device. On a larger patient cohort, these new measured data on skin elasticity, before and after the treatment delivery, could have the potential to predict the development of skin toxicity and implement preventive actions.[36]

In conclusion, ultra-hypofractionated whole-breast radiotherapy, when supported by advanced treatment techniques, is both feasible and safe. No severe adverse effects were observed at any of the different timeframes. Furthermore, no ipsilateral lung, heart, or contralateral breast toxicities were observed, and acute and late skin toxicities were shown to be lower in contrast to data presented in the literature.

Disclosure

Professor Roberto Di Marco reports a patent CUTIBACTERIUM ACNES STRAIN AND ITS MEDICAL USES WO EP CN JP KR AU BR CA CO IL IT MX BR112022015153A2 licensed to WO EP CN JP KR AU BR CA CO IL IT MX BR112022015153A2. The authors report no conflicts of interest in this work.

References

1. Darby S, McGale P, Correa C, et al.; Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Effect of radiotherapy after breast-conserving surgery on 10-year recurrence and 15-year breast cancer death: meta-analysis of individual patient data for 10,801 women in 17 randomised trials. *Lancet*. 2011;378(9804):1707–1716.
2. Brunt AM, Wheatley D, Yarnold J, et al. FAST-forward trial management group. *Radiother Oncol*. 2016;120(1):114–118. doi:10.1016/j.radonc.2016.02.027
3. Brunt AM, Haviland JS, Wheatley DA, et al. Hypofractionated breast radiotherapy for 1 week versus 3 weeks (FAST-Forward): 5-year efficacy and late normal tissue effects results from a multicentre, non-inferiority, randomised, Phase 3 trial. *Lancet*. 2020;395:1613–1626. doi:10.1016/S0140-6736(20)30932-6
4. Meattini I, Palumbo I, Becherini C, et al. The Italian Association for Radiotherapy and Clinical Oncology (AIRO) position statements for postoperative breast cancer radiotherapy volume, dose, and fractionation. *La Radiol Med*. 2022;127(12):1407–1411. doi:10.1007/s11547-022-01563-9
5. Borghero YO, Salehpour M, McNeese MD, et al. Multileaf field-in-field forward-planned intensity-modulated dose compensation for whole-breast irradiation is associated with reduced contralateral breast dose: a phantom model comparison. *Radiother Oncol*. 2007;82:324–328. doi:10.1016/j.radonc.2006.10.011
6. Buwenge M, Cammelli S, Ammendolia I, et al. Intensity modulated radiotherapy for breast cancer: current perspectives. *Breast Cancer*. 2017;9:121–126. doi:10.2147/BCTT.S113025
7. Guerrero M, Li XA, Earl MA, et al. Simultaneous integrated boost for breast cancer using IMRT: a radiobiological and treatment planning study. *Int J Radiat Oncol BiolPhys*. 2004;59(5):1513–1522. doi:10.1016/j.ijrobp.2004.04.007
8. Hijal T, Fournier-Bidoz N, Castro-Pena P, et al. Simultaneous integrated boost in breast conserving treatment of breast cancer: a dosimetric comparison of helical tomotherapy and three-dimensional conformal radiotherapy. *Radiother Oncol*. 2010;94(3):300–306. doi:10.1016/j.radonc.2009.12.043
9. Aly MM, Glatting G, Jahnke L, et al. Comparison of breast simultaneous integrated boost (SIB) radiotherapy techniques. *Radiat Oncol*. 2015;10:139. doi:10.1186/s13014-015-0452-2
10. Macchia G, Cilla S, Buwenge M, et al. Intensity-modulated radiotherapy with concomitant boost after breast conserving surgery: a Phase I–II trial. *Breast Cancer*. 2020;12:243–249. doi:10.2147/BCTT.S261587
11. Corradini S, Ballhausen H, Weingandt H, et al. Left-sided breast cancer and risks of secondary lung cancer and ischemic heart disease: effects of modern radiotherapy techniques. *Strahlenther Onkol*. 2018;194:196–205. doi:10.1007/s00066-017-1213-y
12. Badakhshi H, Kaul D, Nadobny J, et al. Image-guided volumetric modulated arc therapy for breast cancer: a feasibility study and plan comparison with three-dimensional conformal and intensity-modulated radiotherapy. *Br J Radiol*. 2013;86:20130515. doi:10.1259/bjr.20130515
13. Fogliata A, Seppala J, Reggiori G, et al. Dosimetric trade-offs in breast treatment with VMAT technique. *Br J Radiol*. 2017;90(1070):20160701. doi:10.1259/bjr.20160701
14. Cilla S, Macchia G, Romano C, et al. Challenges in lung and heart avoidance for postmastectomy breast cancer radiotherapy: is automated planning the answer? *Med Dosim*. 2021;46(3):295–303. doi:10.1016/j.meddos.2021.03.002
15. Cilla S, Romano C, Macchia G, et al. Automated hybrid volumetric modulated arc therapy (HVMAT) for whole-breast irradiation with simultaneous integrated boost to lumpectomy area: a treatment planning study. *Strahlenther Onkol*. 2022;198(3):254–267. doi:10.1007/s00066-021-01873-3
16. Balaji K, Balaji Subramanian S, Sathiya K, et al. Hybrid planning techniques for hypofractionated whole-breast irradiation using flattening filter-free beams. *Strahlenther Onkol*. 2020;196(4):376–385. doi:10.1007/s00066-019-01555-1
17. Venjakob A, Oertel M, Hering DA, et al. Hybrid volumetric modulated arc therapy for hypofractionated radiotherapy of breast cancer: a treatment planning study. *Strahlenther Onkol*. 2021;197(4):296–307. doi:10.1007/s00066-020-01696-8
18. Wickline MM. Prevention and treatment of acute radiation dermatitis: a literature review. *Oncol Nurs Forum*. 2004;31:237–247. doi:10.1188/04.ONF.237-247
19. Kumar S, Juresic E, Barton M, Shafiq J. Management of skin toxicity during radiation therapy: a review of the evidence. *J Med Imaging Radiat Oncol*. 2010;54:264–279. doi:10.1111/j.1754-9485.2010.02170.x
20. Mangano K, Vergalito F, Mammana S, et al. Evaluation of hyaluronic acid-P40 conjugated cream in a mouse model of dermatitis induced by oxazolone. *Exp Ther Med*. 2017;14(3):2439–2444. PMID: 28962179; PMCID: PMC5609204. doi:10.3892/etm.2017.4810
21. Magnifico I, Perna A, Cutuli MA, et al. A wall fragment of cutibacterium acnes preserves junctional integrity altered by staphylococcus aureus in an ex vivo porcine skin model. *Pharmaceutics*. 2023;15(4):1224. doi:10.3390/pharmaceutics15041224
22. Milani M, Barcella A, Puviani M. Efficacy of a corticosteroid-free, 5% hyaluronic-based facial cream in the treatment of seborrheic dermatitis. a proof-of-concept study. *J Clin Exp Dermatol Res*. 2017;8:6. doi:10.4172/2155-9554.1000426
23. Cilla S, Digesù C, Macchia G, et al. Clinical implications of different calculation algorithms in breast radiotherapy: a comparison between pencil beam and collapsed cone convolution. *Phys Med*. 2014;30(4):473–481. doi:10.1016/j.ejmp.2014.01.002
24. Cancer Therapy Evaluation Program Common Terminology Criteria for Adverse Events version 5.0; 2017.
25. Harris JR, Levene MB, Svensson G, et al. Analysis of cosmetic results following primary radiotherapy for stages I and II carcinoma of the breast. *Int J Radiat Oncol Biol Phys*. 1979;5(2):257–261. doi:10.1016/0360-3016(79)90729-6
26. Haviland JS, Ashton A, Broad B, et al. Evaluation of a method for grading late photographic change in breast appearance after radiotherapy for early breast cancer. *Clin Oncol*. 2008;20(7):497–501. doi:10.1016/j.clon.2008.03.017
27. Aaronson NK, Ahmedzai S, Bergman B, et al. The European organization for research and treatment of cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. *J Natl Cancer Inst*. 1993;85:5253–5526. doi:10.1093/jnci/85.5.365
28. Sprangers MA, Groenvold M, Arraras JI, et al. The European organization for research and treatment of cancer breast cancer-specific quality-of-life questionnaire module: first results from a three-country field study. *J Clin Oncol*. 1996;14:2756–2768. doi:10.1200/JCO.1996.14.10.2756
29. Dobrev H. Use of Cutometer to assess epidermal hydration. *Skin Res Technol*. 2000;6(4):239–244. doi:10.1034/j.1600-0846.2000.006004239.x
30. Nedelec B, Forget NJ, Hurtubise T, et al. Skin characteristics: normative data for elasticity, erythema, melanin, and thickness at 16 different anatomical locations. *Skin Res Technol*. 2016;22(3):263–275. doi:10.1111/srt.12256
31. Yee C, Wang K, Asthana R, et al. Radiation-induced skin toxicity in breast cancer patients: a systematic review of randomized trials. *Clin Breast Canc*. 2018;18:e825e40.

32. Massaccesi M, Caravatta L, Cilla S, et al. Active Breathing Coordinator in adjuvant three-dimensional conformal radiotherapy of early stage breast cancer: a feasibility study. *Tumori*. 2010;96(3):417–423. doi:10.1177/030089161009600307
33. Pietrangelo L, Magnifico I, Guerrera A, et al. LimpiAD foam and the potential control of the pressure ulcers onset. *Biomed Pharmacother*. 2021;144:112327. doi:10.1016/j.biopha.2021.112327
34. Pietrangelo L, Dattola A, Magnifico I, et al. Efficacy and microbiota modulation induced by LimpiAL 2.5%, a new medical device for the inverse psoriasis treatment. *Int J Mol Sci*. 2023;24(7):6339. doi:10.3390/ijms24076339
35. Bonaparte JP, Ellis D, Chung J. The effect of probe to skin contact force on BCutometer MPA 580 measurements. *J Med Eng Technol*. 2013;37:208e12. doi:10.3109/03091902.2013.779325
36. Cilla S, Romano C, Macchia G, et al. Machine-learning prediction model for acute skin toxicity after breast radiation therapy using spectrophotometry. *Front Oncol*. 2023;12:1044358. doi:10.3389/fonc.2022.1044358

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