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ORIGINAL ARTICLE

Computational Model Based on Optical Coherence Tomography (OCT) Skin Scanning to Identify and Quantify Acute Radiation Dermatitis (ARD): A Prospective Diagnostic Study

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KEYWORDS

Acute radiation dermatitis;
Radiodermatitis;
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OCT;
Radiotherapy;
Breast cancer

Abstract

Background: Acute radiation dermatitis (ARD) is the most widely reported radiotherapy-induced adverse event. Currently, there is no objective or reliable method to measure ARD.

Objective: Our main objective was to identify and quantify the effects of radiotherapy with a computational model using optical coherence tomography (OCT) skin scanning. Secondary objectives included determining the ARD impact of different radiotherapeutic schemes and adjuvant topical therapies.

Methods: We conducted a prospective, single-center case series study in a tertiary referral center of patients with breast cancer who were eligible for whole breast radiotherapy (WBRT).

Results: A total of 39 women were included and distributed according to the radiotherapeutic schemes (15, 20, and 25 fractions). A computational model was designed to quantitatively analyze OCT findings. After radiotherapy, OCT scanning was more sensitive revealing vascularization changes in 84.6% of the patients (vs 69.2% of the patients with ARD by clinical examination). OCT quantified an increased vascularization at the end of WBRT ($P < .05$) and a decrease after 3 months ($P = .032$). Erythematous skin changes by OCT were more pronounced in the 25-fraction regime.

Conclusion: An OCT computational model allowed for the identification and quantification of vascularization changes on irradiated skin, even in the absence of clinical ARD. This may allow the design of standardized protocols for ARD beyond the skin color of the patients involved.

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PALABRAS CLAVE

Radiodermatitis
aguda;
Tomografía de
coherencia óptica;
TCO;
Radioterapia;
Cáncer de mama

Modelo computacional basado en la tomografía de coherencia óptica (TCO) para identificar y cuantificar la radiodermatitis aguda (RA): estudio observacional prospectivo

Resumen

Antecedentes: La radiodermatitis aguda (RA) es el efecto adverso más común de la radioterapia. Actualmente, no existe un método objetivo y reproducible para medir RA.

Objetivo: El objetivo principal es identificar y cuantificar los efectos de la radioterapia en la piel mediante tomografía de coherencia óptica (TCO) usando un modelo computacional. Los objetivos secundarios son determinar el grado de RA según diferentes esquemas de radioterapia y el efecto del tratamiento tópico adyuvante.

Métodos: Estudio de serie de casos prospectivo unicéntrico de pacientes con cáncer de mama candidatas a radioterapia.

Resultados: Treinta y nueve mujeres fueron incluidas y distribuidas según el esquema de radioterapia de 15, 20 y 25 fracciones. Se diseñó un modelo computacional para analizar cuantitativamente los hallazgos de la TCO. Después de la radioterapia, la exploración TCO fue más sensible y mostró cambios en la vascularización en el 84,6% de los pacientes (frente al 69,2% de los pacientes con signos clínico-dermatoscópicos de RA). La TCO cuantificó un aumento en la vascularización al final de la radioterapia ($p < 0,05$) y una disminución después de 3 meses ($p = 0,032$). Los cambios en el eritema por TCO fueron más pronunciados en el régimen de 25 fracciones.

Conclusión: Un modelo computacional basado en TCO permite la identificación y cuantificación de los cambios de vascularización en la piel irradiada, incluso en ausencia de RA clínica. Esto puede permitir el diseño de protocolos estandarizados para RA más allá del color de la piel de los pacientes.

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Introduction

Breast cancer is the most prevalent malignancy worldwide with 1 out of every 4 malignancies reported in women.¹ For women with early-stage breast cancer, adjuvant breast radiation therapy is an essential component of breast-conserving therapy and has been shown to decrease local recurrences and improve the overall survival.^{2–4} Whole breast irradiation (WBI) was previously performed using a standard 5-week fractionated schedule with a total dose of 50 Gy. However, 3 large randomized clinical trials have shown that hypofractionated WBI, with a total dose of 40.05–42 Gy, achieves equivalent local disease control and cosmetic outcomes vs standard fractionation. Therefore, a 3-week hypofractionated WBI regimen is now considered the standard of care for women with early-stage, node negative, operable breast cancer.^{4,5} Furthermore, the addition of a radiation boost to the tumor bed is an important component of adjuvant therapy, improving local control over WBI alone.^{6,7}

Despite these new developments, acute or chronic skin toxicity is still a common finding (80–90% of the patients), with unpredictable severity and progression.^{8–10} This has prompted several attempts to find the best therapeutic and prophylactic topical therapy for acute radiation dermatitis (ARD). However, the management of ARD is not firmly based on scientific evidence, since there is no standardization of treatment and multiple agents have been proposed (aloe-vera, sucralfate, steroids, trolamine, hyaluronic acid, biaffine, calendula, chamomile, almond oil, vitamin C, etc.).^{8,10–17}

Different grading scales for ARD have been developed (RTOG, NCI CTCAE, LENT/SOMA).^{18–20} However, all of them are somewhat subjective and difficult to replicate.^{21–24} The optical coherence tomography (OCT) is a non-invasive imaging modality based on low coherence interferometry that provides in vivo imaging and detailed pictures of subsurface tissue micro-structures down to a depth of 2 mm with a real-time resolution of 4–10 μm . The OCT can be used to acquire images from the derman and epidermal layers of the skin, skin appendages, and blood vessels. In addition, dynamic-OCT (D-OCT) allows for the detection of blood flow in vivo and visualization of skin microvasculature.²⁵ Therefore, the OCT allows for the study of a continuous process such as wound healing and vascularization,²⁶ and could be a promising tool in the management and research of several skin conditions.^{27,28}

The primary endpoint of the study was to demonstrate the usefulness of OCT scanning in measuring radiotherapy-induced skin changes. Secondary endpoints were to compare the degree of ARD between different radiotherapy regimes, and to assess the tolerability of a standardized topical therapy.

Material and methods

Study design

This was a prospective and observational study to evaluate the skin changes observed by clinical examination and

dermoscopy and OCT imaging by dynamic skin scanning in consecutive patients diagnosed with breast cancer from a tertiary referral center and on standard radiotherapy in 3 different schemes (15, 20, or 25 fractions).

In addition to the general recommendations, to standardize the cohort, a hypoallergenic restorative cream, containing copper and zinc sulfate and a postbiotic repairing ingredient C+ Restore[®] was used on the target areas on a daily basis until 1 month after finishing radiotherapy.¹ All adverse events, including ARD, were recorded during and 3 months after radiotherapy.

Study population

Volunteer patients aged 18 and over who were breast cancer candidates for radiotherapy according to the radio-oncologist regular scheme from a tertiary referral center. Inclusion date: from January 2020 to July 2021, until, at least, 10 patients from each fractionation group were included. Data collection was concluded in November 2021. All patients signed an informed consent form, and the study was approved by Hospital Clínic de Barcelona research ethics committee (registration HCB/2019/0796).

The 3 breast radiotherapy schemes used were a hypofractionated scheme with a total dose of 40.05 Gy in 15 fractions (2.67 Gy/fraction) (scheme-15), the same hypofractionated scheme plus a sequential boost on the surgical bed for a total dose of 13.35 Gy in 5 fractions (2.67 Gy/fraction) (scheme-20), and breast and regional lymph nodes radiotherapy in a normo-fractionated scheme plus concomitant boost for a total dose of 57.5 Gy in 25 fractions (2.30 Gy/fraction) (scheme-25).

Interventions and assessments

Patients were closely monitored by the dermatology and radiation oncologist to ensure early detection of skin toxicity in the irradiated field. All previous dermatological skin condition were ruled out. Participants were evaluated clinically, through dermoscopy and OCT-scanning at 3 different points in time: before (t0), at the end (maximum dose received, tF) and 3 months after the end of radiotherapy (t+3m). A window margin of ± 3 days in tF and ± 7 days in t+3m was permitted. Both breasts (treated and non-treated) were systematically examined and registered by clinical and dermoscopy images of 25 mm \times 25 mm areas, and OCT mosaics (6 mm \times 6 mm) to cover the 4 quadrants of both breasts. The non-irradiated breast was systematically used as an internal control. [Supplementary figures \(Fig. S1\)](#) show an example of the dynamic information obtained by OCT.

The grade of ARD was categorized based on the Common Terminology Criteria for Adverse Events (CTCAE) scale (grade 0: absence of perceptible lesions, grade I: presence of mild erythema, dry peeling; grade II: presence of moderate-to-mild erythema, irregular wet peeling, confined mainly to skin folds and wrinkles, moderate edema; grade III: presence of wet peeling in areas other than skin folds or wrinkles; bleeding induced by minor trauma or abrasion; and grade IV: presence of skin necrosis or ulcers).

Prior to radiotherapy, the patients' baseline functional condition, symptoms, and overall performance status were evaluated through a quality-of-life questionnaire (EORTC QLQ-C30).²⁵ At the end of the study, patients' skin tolerance was measured using a standardized test (dermatological-level quality of life; DLQI).

Statistical analysis

SPSS with python and statistical and image processing libraries (statsmodel, opencv, skimage, and numpy) were used to perform the statistical analyses. ANOVA and the Chi-square test were used to assess inter-group differences between quantitative and qualitative variables. To compare OCT determinations, we first normalized the intra-patient measurements using the 1st acquisition of each breast (non-irradiated). Then, we computed the differences in the vascularization biomarker at the 2 posterior points in time and computed the statistical differences between acquisitions using the *t*-test.

Results

Study population and baseline features

Eleven out of the 59 patients invited to participate refused to do so, 9 were lost to the follow-up due to the COVID-19 lockdown, and 39 were included and completed the *per protocol* analysis ([Fig. 1](#)). [Table 1 \(see supplementary material\)](#) shows the demographic data of the participants included.

Overall, the patients' mean age was 58.5 years, they had a predominantly light phototype (I–III, 76.92%) and were non-smokers (79.49%). Regarding radiotherapy schemes, 38.46% of the patients received scheme-15; 35.89%, scheme-20; and 24.64%, scheme-25. Statistically significant differences were reported among the different radiotherapy groups in terms of age (older in scheme-25; $P = .0078$) and body mass index (BMI) (higher in scheme-25; $P = .0392$). No significant differences were seen based on the skin phototype, smoking status, or functional baseline performance status.

Radiotherapy-induced dermatological changes

Clinical examination and dermoscopy allowed for the detection of ARD in 69.2% of the patients. At the end of the therapy (tF), 12 patients (30.8%) did not show ARD, 25 patients (64.1%) had grade 1 ARD, and 2 patients (5.1%) presented with grade 2 ARD. No patient presented grade 3–4 toxicity. At t+3m, patients did not show any clinical or dermoscopically measurable changes ([Fig. 2](#)).

OCT scanning evaluation

A novel computational model was designed to process OCT volumes and detect the amount of blood on the OCT image from the sample. OCT imaging could detect differences in terms of skin vascularity and quantify the amount of blood in every volume. Through a series of computer vision techniques, we drew the vascularized regions. Briefly, we first

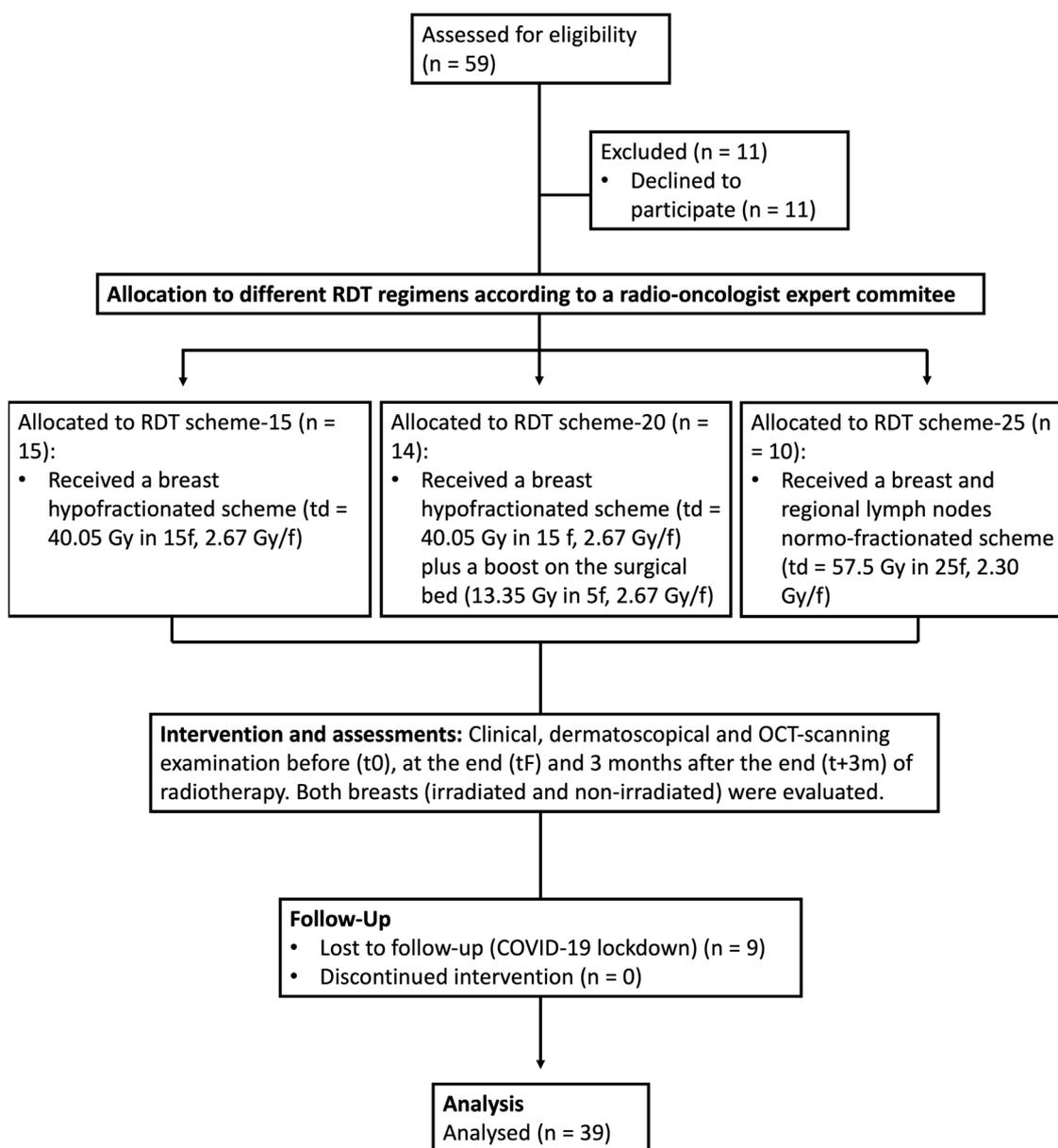


Figure 1 Study flowchart. Abbreviations: Td, total dose; f, fractions.

223 used a color-based separation to draw blood circulation from
 224 the volume and skin's structures. Then, a series of morpho-
 225 logical techniques based on dilating and eroding operators
 226 were used to eliminate any acquired noise at the frame
 227 level. Finally, the volumetric information was added and
 228 filtered to eliminate any noise triggered by the patient's
 229 unintentional movements. The sum of the red pixels in the
 230 image was then used as the quantifiable biomarker for ery-
 231 themia (and vascularization) in an OCT Volume.
 232 First, a comparative approach was made by studying
 233 the skin changes of each patient on the irradiated vs
 234 non-irradiated breast at the end of radiotherapy (tF). Quan-
 235 titative analyses showed a statistically significant increase
 236 of erythema after (tF) ($P < .05$) irradiating fields (Fig. 3A).
 237 Second, the process was repeated 3 months after treatment
 238 completion (t + 3m). The results showed a statistically rel-

239 evant decrease of erythema ($P = .032$) in irradiated fields
 240 (Fig. 3A).
 241 Each breast was also compared to itself at baseline (t0)
 242 at different time points; at tF the irradiated breast showed a
 243 significant increase in the erythema index ($P = .024$) (Fig. 3B)
 244 and a decrease in the erythema index at t + 3m ($P = .07$)
 245 (Fig. 3B). In this regard, the OCT imaging revealed statis-
 246 tically significant differences in terms of vascularization of
 247 treated breasts.
 248 Overall, at the end of radiotherapy (tF), almost all
 249 patients (33 out of 39) showed a significant increase in their
 250 erythema index according to the OCT (Figs. 3B and 4), while,
 251 at t + 3m, irradiated breasts showed a significant decrease of
 252 the erythema index (Figs. 3B and 4). As for the not-irradiated
 253 breasts evaluated at the 3 different points in time, no sig-
 254 nificant differences were found (Fig. 3C).

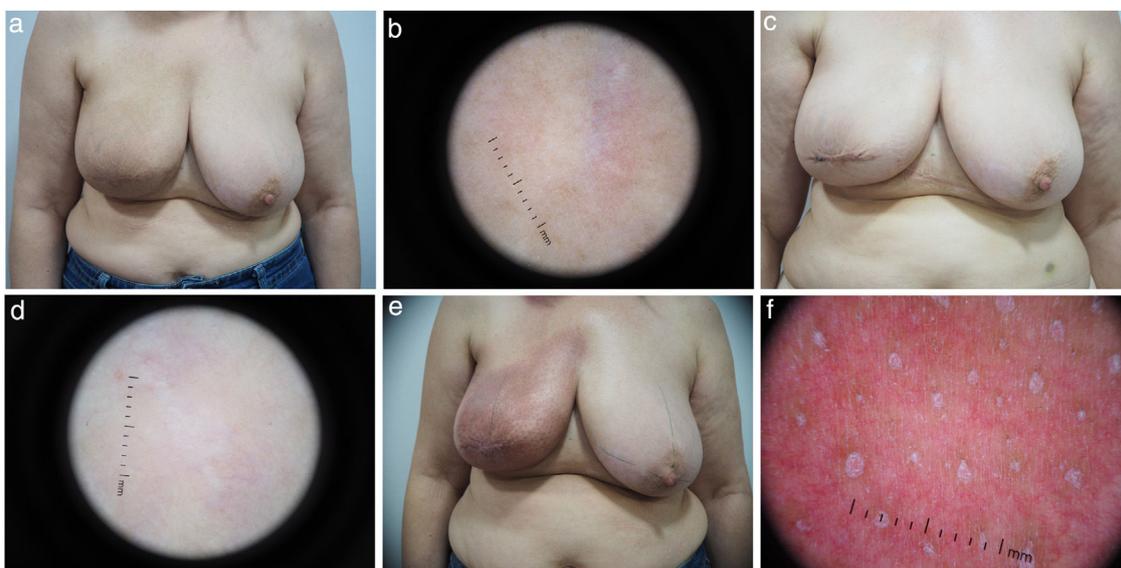


Figure 2 Clinical and dermoscopic images of a patient with breast cancer on radiotherapy with grade 2 ARD before (a, b), at the end of (c, d), and 3 months into (e, f) radiotherapy.

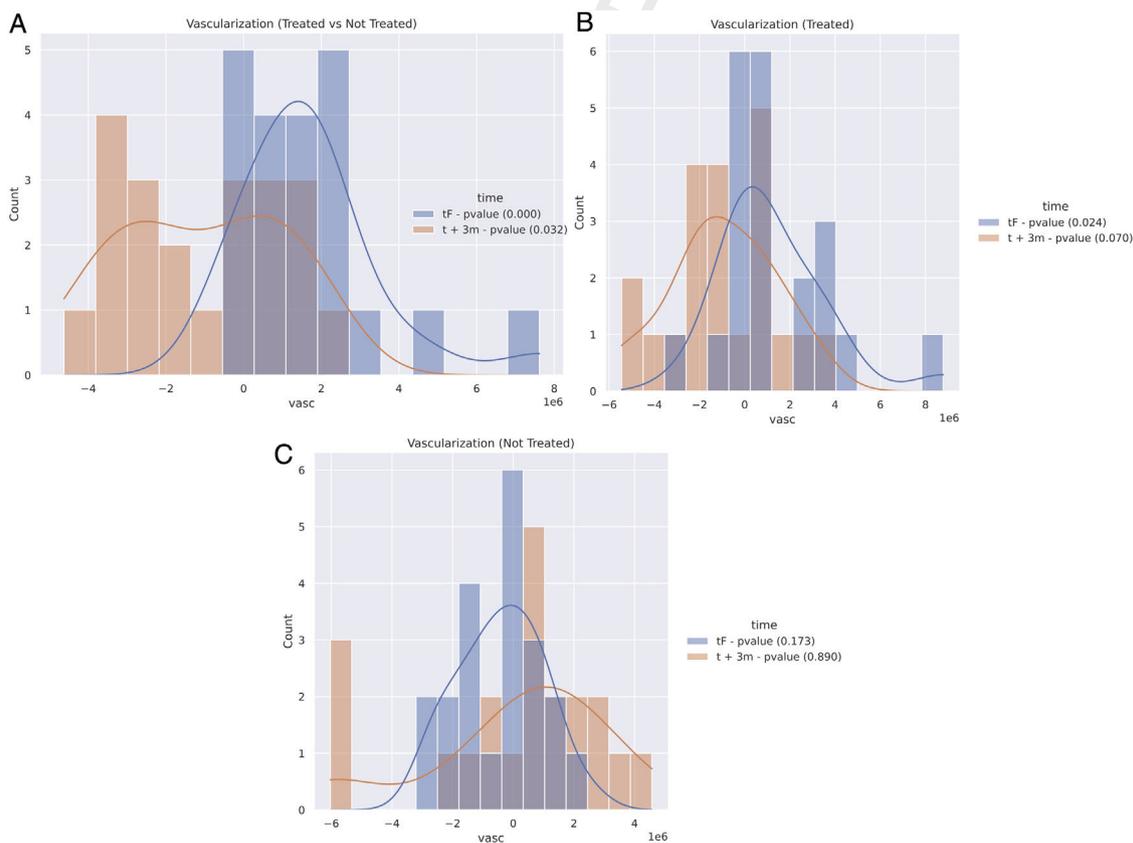


Figure 3 Quantitative results of OCT imaging vascularization of the entire cohort. Positive numbers reflect a higher blood volume than the comparative sample. Negative numbers are indicative of a decreased flow. Treated and not-treated breasts reflect the comparison between the breast that received radiation, and the contralateral one which did not at that time. A: Comparison between treated and non-treated contralateral breasts at the tF (blue: end of therapy) and t + 3m points in time (orange: 3 months after end of therapy). B: Comparison of the treated breasts at the tF (blue) and t + 3m points in time (orange) vs t0 (baseline). C: Comparison of non-treated breasts at tF (blue) and t + 3m points in time (orange), compared to t0.

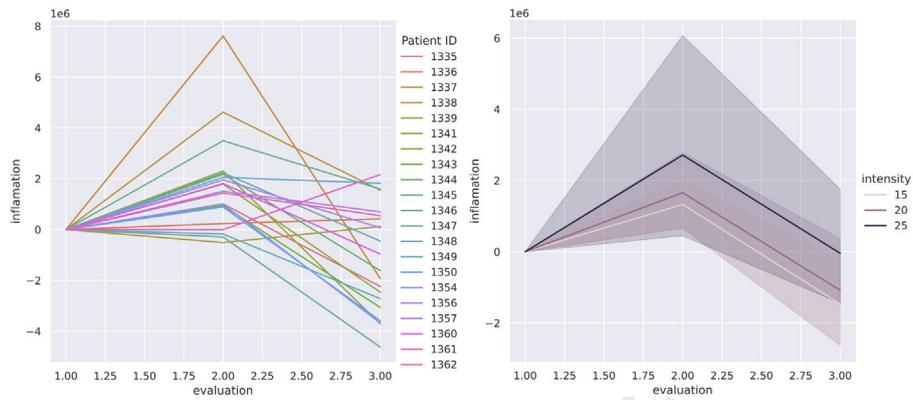


Figure 4 Evolution of vascularization with radiotherapy measured quantitatively with OCT imaging across different radiotherapy fractionation schemes. A: Vascularization changes of all cohort samples at the beginning of RT (t0), at the end (tF), and 3 months later (t + 3m). B: Vascularization mean changes comparing the 3 radiotherapy scheme regimes: 15- (light pink), 20- (dark pink) and 25-fraction (black) schemes.

255 Vascularization changes by OCT through radiotherapy
256 treatment (t0, tF and t + 3m) were also compared across the
257 3 different radiotherapy scheme protocols (15, 20 and 25
258 fraction regimes) (Fig. 4). The OCT clearly showed quantitative
259 differences between regimes in terms of mean change
260 to the erythema index (Fig. 4B). Scheme-25 triggered the
261 highest intensity changes to the erythema index, with a significant
262 increase at tF. At t + 3m, the shortest regime (15
263 fractions) reached the most prominent decrease of the erythema
264 index vs the longest treatment (25 fractions) which
265 showed the lowest decrease of the erythema index (Fig. 4B).

266 Quality of life and tolerance of adjuvant therapy

267 No adverse events associated with the OCT imaging tests or
268 topical adjuvant therapy were ever reported. All patients
269 showed an excellent tolerance to the adjuvant repairing
270 cream. None of them abandoned the daily routine of using
271 the adjuvant therapy on the irradiated areas.

272 Discussion

273 ARD is the most common adverse event associated with
274 breast radiotherapy. Despite being usually of mild-to-
275 moderate intensity, it can impact the patients' quality of life
276 tremendously putting the completion of the radiotherapy
277 protocol at risk.²² Currently, the most widely used categorizations
278 of ARD are subjective clinical scales based on skin changes
279 perceived by the naked eye, which are difficult to replicate and
280 quantify.²¹ The lack of an objectively quantifiable assessment
281 of ARD poses significant challenges such as accurately predicting
282 the grade of skin toxicity, the development of chronic radiation
283 dermatitis, and measuring the effect of adjuvant topical therapies.
284 The present study demonstrates that non-invasive OCT skin
285 scanning detects statistically significant changes to irradiated
286 skin after radiotherapy through a new objective quantitative
287 computational erythema index.

289 As shown in this study, clinical examination could barely
290 classify ARD as grade 0, 1 or 2 with very subtle differences
291 between each group. In addition, dermoscopy was not sensitive
292 enough to identify changes to the skin and almost

293 one third of the patients did not present any changes. Conversely,
294 through a specifically designed algorithm of OCT dynamic images,
295 we could detect and quantify the changes induced in various
296 irradiated areas even when the clinical examination could not
297 perceive such differences. Comparative analysis with the non-
298 irradiated breast proved that these changes are solely observed
299 in the treated areas. These results support the view that the
300 differences seen on the OCT in the irradiated breast are real
301 and not due to measurement artifacts or physiological changes.
302 Therefore, OCT skin scanning allows for the quantitative
303 measurement of erythema associated with radiotherapy-induced
304 skin changes.

305 Secondly, the OCT images were able to demonstrate that
306 vascularization changes reach their maximum level of intensity
307 toward the end of radiotherapy with the highest increase in
308 the erythema index vs baseline and 3 months after radiotherapy.
309 At this point, the skin has received the total radiation dose,
310 and the healing process is still at the beginning. The most
311 prominent changes were seen in scheme-25: patients with a
312 higher risk of locoregional recurrence who, consequently, receive
313 breast and regional lymph node radiotherapy.

314 Additionally, 3 months after finishing radiotherapy, the
315 OCT images revealed a significant decrease in the erythema
316 index of the target areas in all groups, even vs baseline
317 non-treated skin. Therefore, observed changes seem to be
318 mostly reversible and only focused on irradiated areas.
319 Interestingly, the shortest radiotherapy scheme (scheme-15)
320 showed a more prominent decrease of the erythema index
321 at the end of therapy.

322 Previously, studies have explored the development and
323 implementation of objective methods for assessing vascularization,
324 inflammation, and radiotherapy-induced fibrotic changes to
325 the skin (hyperspectral imaging, thermal imaging, laser Doppler
326 flowmetry, reflection spectrophotometry, tissue oxygenation).
327 Unfortunately, such techniques have had limited success and
328 have not been implemented in the everyday practice.³⁰ Recently,
329 a prospective study evaluating ARD with reflectance confocal
330 microscopy (RCM) showed that exocytosis, spongiosis, disarrayed
331 epidermis and abnormal dermal papillae were frequently present
332 in ARD and correlated with the degree of severity of ARD.³¹
333 Among the

336 non-invasive imaging modalities used to evaluate the skin,
337 the OCT may provide an ideal balance between resolution
338 and depth, along with the dynamic mode to measure vas-
339 cularization changes. One of the main OCT applications in
340 dermatology has been the study of fibrotic disorders²⁶ since
341 orientation, organization, and the reflective properties of
342 skin collagen render the tissue birefringent and detectable
343 to the OCT. Regarding ARD, Photiou et al. showed that
344 weekly imaging with OCT of irradiated skin could detect
345 early ARD with accuracy rates of up to 88.3%.³²

346 Multiple former studies have tried to demonstrate the
347 benefits of using a specific adjuvant therapy; however, the
348 lack of objective measurements of the effects is a main lim-
349 itation of such studies.^{8,21} In an attempt to standardize ARD
350 prevention and treatment in our cohort, we used a hypoal-
351 llergenic restorative protective cream containing copper and
352 zinc sulfate and a postbiotic repairing ingredient C+ Restore®
353 which was well tolerated.

354 As for the limitations of this study, it is a single-center
355 study with a short follow-up. On the other hand, since the
356 OCT is a novel non-invasive imaging modality, it is not widely
357 available in all hospitals. Therefore, the use of OCT in the
358 routine clinical practice is, currently, limited. Regarding the
359 therapeutic effect of the applied cream, this study was of a
360 small sample and no randomized arm was ever included.
361 Therefore, we could not properly explore any treatment
362 effects or draw any conclusions. Finally, age and body mass
363 index (BMI) were not homogeneously distributed amongs the
364 different radiotherapy groups, which could have impacted
365 our results. This was an expected bias though since younger
366 patients (< 60 years) almost always receive a boost scheme,
367 whereas in older patients (>60 years), usually of a higher
368 BMI, the boost scheme is usually indicated only in cases of
369 high-risk tumors.

370 Conclusions

371 This study is the first prospective study ever conducted
372 on a new computational algorithm of noninvasive OCT
373 skin imaging to detect and quantify the effects of
374 radiotherapy-induced microvasculature. The OCT revealed
375 vascularization changes even in the absence of other clin-
376 ical signs. More intense and longer radiotherapy schemes
377 showed more prominent vascular changes, though mostly
378 reversible after 3 months on radiotherapy. Future stud-
379 ies should explore if late-onset adverse events associated
380 with radiotherapy in terms of scarring and fibrosis could be
381 detected early on with the OCT be associated with persistent
382 increased vascularization. This study could be a preliminary
383 step for the standardization of the determination, gradu-
384 ation, and classification of ARD. Importantly, this method
385 could also take into consideration the existing diverse eth-
386 nicity, especially that in which redness is not visible and
387 could objectively assess the impact of different preventive
388 measures.

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Conflict of interests

The authors declare that they have no conflict of interest.

Uncited reference

29.

Appendix A. Supplementary data

Supplementary data associated with this arti-
cle can be found, in the online version, at
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