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Tamoxifen-induced ocular alterations: a multimodal imaging study

Valutazione delle alterazioni oculari in corso di terapia con Tamoxifene con studio imaging multimodale

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Introduction

Newer anticancer drugs have revolutionized cancer treatment in the last decades; in fact, they are based on the concept of precision medicine, with identification of a particular target that drives the oncogenesis and a selective inhibition with a specific drug (the target therapy). Moreover, combination therapy and newer methods of delivery aim to increase their efficacy while minimizing toxicities.

Retina has got a very high metabolic activity and the choroid is highly vascularized, contributing to the majority of oxygen and other nutrients supply to the outer retina and the retinal pigment epithelium (RPE); therefore these structures may represent targets of toxicity of anticancer drugs.[1]

The eye has a unique structure, but its surface molecules, cytokines, and immune responses are similar to those in the brain. Moreover, the inner blood-retina barrier (BRB) presents similarities to the blood brain barrier (BBB), and the eye may represent a window to evaluate neurological disorders and to study the effects of drugs penetrating the central nervous system.[2]

Newer ophthalmological imaging modalities have enabled noninvasive optical biopsy (optical coherence tomography, OCT), with high-resolution reconstructions of retinal anatomy in a rapid and reproducible fashion, and sophisticated angiography techniques allow in-depth evaluation of retinal and choroidal vasculature even without intravenous injection of a dye (OCT angiography, OCT-A).[3-5]

In 2020 2.3 million women were diagnosed with breast cancer and it caused 685000 deaths globally.[6] As of the end of 2020, 7.8 million women alive were diagnosed with breast cancer in the past 5 years, making it the world's most prevalent cancer.[7]

Breast cancer represents an important global health burden, as it is estimated to be the most common cancer diagnosis and one of the most important cancer-related causes of death in the female population.[8]

Breast cancer started showing improvements in survival rates in the 1990s, when countries established breast cancer early detection programmes and comprehensive treatment programs including effective medical therapies.

Treatment for breast cancer depends on the subtype of cancer and how much it has spread outside of the breast to lymph nodes or to other parts of the body.[9-10]

Medicines to treat breast cancers are selected based on the biological properties of the cancer as determined by tumor marker determination, and they may be given before (neoadjuvant) or after (adjuvant) surgery, leading to a treatment that is based on the biological subtyping of the cancer.

The hormones estrogen and progesterone are produced by the ovaries in premenopausal women and by some other tissues, including fat and skin, in both premenopausal and postmenopausal women and in men.

These hormones also promote the growth of some breast cancers, which are therefore called hormone-sensitive (or hormone-dependent) breast cancers.

Sampling of tumor tissue that has been removed by surgery allows to identify cancers that express the estrogen receptor (ER) and/or the progesterone receptor (PR).

Up to 80% of breast cancers in women are ER positive or PR positive, while approximately 90% of breast cancers in men are ER positive and 81% are PR positive.[11-12]

Hormone therapy slows or stops the growth of hormone-sensitive tumors by blocking the body's ability to produce hormones or by interfering with the effects of hormones on breast cancer cells. Hormone therapy may be therefore used to treat hormone-sensitive breast cancer as an adjuvant therapy for early-stage breast cancer, as a neoadjuvant treatment, and

to treat advanced or metastatic breast cancer. Various endocrine treatment strategies exist, including ovarian suppression, aromatase inhibitors and Tamoxifen.[13]

Tamoxifen is a selective estrogen receptor modulator (SERM) that competes with estradiol in binding to estrogen receptors, inhibiting the binding of the receptor to the estrogen-response element on DNA.[14-15] Tamoxifen also promotes upregulation of transforming growth factor B (TGF-B) and downregulation of insulin-like growth factor 1 (IGF-1), playing a significant role in suppression of tumor cells growth, particularly in breast cancer.[16] SERMs are a group of nonsteroidal agents that produce estrogen-like effects on some tissues and antiestrogen-like effects on some other tissues (such as the breast). SERM targets include any tissue that possesses estrogen receptors, including breast, uterus, bone, liver, vasculature, and brain.[17]

Tamoxifen is typically used to treat patients with ER-positive breast cancer and as a preventive treatment in high-risk patients.[18-19] It is usually taken for 5 to 10 years in a daily dose of 20 mg, with increased survival rates and reduced recurrence at 10 years of treatment.

Despite its many indications, and like all pharmacologic therapies, Tamoxifen is not without side effects. In fact, uterine cancer, deep vein thrombosis, pulmonary embolism and stroke have all been associated to Tamoxifen use; moreover, Tamoxifen has also been known to cause modifications in blood cell counts, irregular menstruation, hot flashes, vaginal discharge, hypertension, nausea, vomiting, and edema, among other side effects.

Limited attention, however, has been given in the literature to the ocular side effects of Tamoxifen therapy.

In the eye, neural retina and RPE are also estrogen receptor-positive tissues that may be affected during the course of Tamoxifen therapy.

Ocular toxicity was first described in female breast cancer patients who received very high doses of Tamoxifen, but subsequent reports found that ocular toxicity can also occur with low-dose Tamoxifen treatment; the prevalence of Tamoxifen-related ocular side effects has been found to be up to 12%.[20]

Several ocular adverse effects have been reported in the literature, including ocular surface disorders, cataract, retinopathy, and optic neuropathy.[21]

Ocular surface disorders may manifest as dry eye, keratopathy, paracentral corneal opacities, or subepithelial deposits. Posterior subcapsular opacities were reported more frequently in Tamoxifen-treated patients.

Retinopathy is the most known and well-studied ocular adverse effect of Tamoxifen therapy.

Characteristic findings of Tamoxifen retinopathy include refractile crystalline deposits on fundus evaluation and hyporeflective foveal cavitations and focal disruption of the photoreceptor layer detected by means of OCT.[22]

Most previous studies on the prevalence of Tamoxifen retinopathy were based only on fundus examinations, without the use of new and non-invasive instruments like OCT and OCT-A, that allow to evaluate early and subtle changes in retinal and choroidal architecture, providing detailed visualization of the tissues and of the vascular networks in the eye.

The presence of subclinical structural chorioretinal findings related to Tamoxifen intake is not well studied and could give important clues regarding the pathophysiology and early recognition of Tamoxifen toxicity.

Tamoxifen and ocular toxicity

Ocular toxicity resulting from Tamoxifen was reported first by Kaiser-Kupfer and Lippman in female breast cancer patients who received high doses of Tamoxifen, more than 120 mg per day.[23] Corneal alterations and retinal changes were described, with a significant decrease in visual acuity as the result of retinopathy, primarily affecting the macular region, accompanied by macular edema.

Subsequent papers reported that ocular toxicity can also occur with regular use of low-dose Tamoxifen treatment (10-20 mg/day).[24] Tamoxifen-related ocular side effects have been recently described in up to 12% of the treated patients.[20] Moreover, a wide range for the time of exposure before development of Tamoxifen-related ocular side effects has been described in the literature, from 3 weeks to 13 years.[22]

In order to understand the side effects of Tamoxifen its pharmacokinetics should be first taken into account. Tamoxifen is generally taken orally in doses of 20 mg/day for 5 to 10 years, with a bioavailability of approximately 100%.[15, 25] Once in the bloodstream, Tamoxifen undergoes complex metabolism, primarily via the cytochrome P450 system. Several primary and secondary metabolites exhibit more antiestrogenic effects in breast cancer cells than Tamoxifen itself. Tamoxifen has a half-life of approximately 5-7 days and it is eliminated predominantly by glucuronidation followed by excretion into the biliary tract.[26] Moreover, ocular penetration of oral Tamoxifen has been documented [27], with the drug found to have penetrated into both vitreous and aqueous cavities, despite the fact that drug levels in aqueous and vitreous did not appear to correlate with serum levels.

Detectable levels of Tamoxifen in the vitreous and aqueous humor suggest an alteration of blood-ocular barriers. In the absence of pathology, barriers such as the BRB are not permeable to macromolecules such as Tamoxifen.[28] It is currently unclear how much of the damage that allows Tamoxifen to exit blood vessels in the eye is due to vascular injury induced by Tamoxifen itself and how much is due to unrelated vasculopathy.[29]

The pathogenetic mechanisms of Tamoxifen-induced ocular toxicity are not completely understood yet. A combination of abnormal lipid metabolism, neurotoxicity, Müller cell dysfunction, decreased estrogen concentration and altered blood flow has been proposed to play a role in Tamoxifen-induced ocular toxicity, although the exact mechanisms of disease remain unclear.[22,29]

Moreover, retinal damage is thought to be caused through multiple mechanisms, including direct toxicity to retinal cells and off-target effects on RPE and Müller glia.

Tamoxifen seems to induce accumulation of drug polar lipid complexes in the lysosomes, a known side effect of various cationic amphiphilic drugs (e.g., chlorpromazine, amiodarone, etc.) with similar structure to Tamoxifen.[30]

The production of drug-lipid complexes inhibits normal catabolism of lipids in the lysosomes, inducing cell oxidative damage.[31] Of note, patients with a high BMI and hyperlipidemia were recently found to be significantly more likely to be affected by Tamoxifen retinopathy.[20] An increased oxidative stress on the retinal tissue, exerted by stable, quinone metabolites of Tamoxifen, has also been found in the literature.[32]

Tamoxifen suppresses sphingolipid metabolism[33] and a chronic retinal damage following Tamoxifen-induced impairment of sphingolipid metabolism may be involved in the pathogenesis of findings associated with patients taking Tamoxifen.

Moreover, Tamoxifen affects RPE cells inhibiting phagocytosis of the rod's outer segments by RPE cells due to lysosomal destabilization, leading to Tamoxifen-induced cell death[34-35].

Another important aspect is that Tamoxifen has been reported to inhibit the glutamate transporter of glial cells[36], therefore it may also affect glutamate uptake of Müller cells, resulting in Müller cell dysfunction followed by neuronal and vascular pathologic features.
Excessive intracellular glutamate build-up results in Müller cell dysfunction and apoptosis, and this leads to vascular remodeling and neurodegeneration of the retinal layers.[37] A reduced glutamate uptake in an RPE cell line has also been found to be caused by Tamoxifen[38], leading to neuronal degeneration.
These mechanisms might explain the propensity for central macular disease in Tamoxifen retinopathy, where both blood flow (and therefore drug levels) and Müller cell density are the greatest.[39]
Morphologic similarities exist between the findings of the patients with Macular Telangiectasia Type 2 (MacTel 2) and those with Tamoxifen retinopathy [40].
Given that Müller cell dysfunction is a major contributor to pathologic features in
eyes with MacTel 2[41] and because the processes of Müller cells are entwined to the retinal vasculature, it is likely that their dysfunction is associated with telangiectasias observed in these retinal diseases. Müller cells also interact closely with retinal neuronal cells and Müller cell degeneration is accompanied by loss of neurons, resulting in edema in the inner or outer retinal layers.[42]
Moreover, choroidal changes were reported during Tamoxifen treatment [43-44], and a possible impairment of choroidal blood flow in the long term could have a deleterious impact on the RPE and photoreceptors and help explain Tamoxifen-induced retinopathy.
Ocular toxicity caused by Tamoxifen is also supposed to be due to its pharmacological effects on estrogen receptors; despite this, other selective estrogen-receptor modulators and aromatase inhibitors do not seem to have nearly as much reported toxicity as Tamoxifen.[45]

Tamoxifen and Cataract

Five or more years of Tamoxifen treatment were found to increase cataract risk[46], with an increased risk of posterior subcapsular cataract development.[47] Other studies detected no increased risk of cataract among breast cancer patients who were treated with Tamoxifen compared to women with other cancers who were not prescribed Tamoxifen.[48]
Animal experiments have shown that rats fed Tamoxifen develop cataracts.[49] Moreover, it was found that chloride channels in the lens of the eye are essential for maintaining normal lens hydration and transmittance, that Tamoxifen blocks these channels (this blockade appears to be independent of the interaction of Tamoxifen with the estrogen receptor), and that, in organ culture, Tamoxifen induces lens opacity.[50]
Despite the fact that research on this topic is still ongoing, breast cancer patients treated with Tamoxifen should be advised of the possibility of cataract development, have a thorough baseline ophthalmic evaluation within the first year of initiating Tamoxifen therapy and receive appropriate follow-up evaluations.

Tamoxifen Optic Neuropathy

Disturbances of the optic nerve caused by Tamoxifen do not appear to be common; optic neuritis appears to have a prevalence ranging from 0.02 to 1.5 %.[51]
Clinically evident optic neuritis resulting from Tamoxifen use has been reported in various papers[21, 52-54], but the optic nerve may often be affected at a subclinical level.
Tamoxifen-related optic nerve toxicity tends to occur bilaterally, after different periods of treatment, with optic disc edema or no clinically visible changes. In these cases, Tamoxifen treatment cessation is reported to result in restoration of visual acuity and most of the visual field defects. Tamoxifen-induced block of swelling–activated chloride channels might be the cause for swelling at the level of optic nerve head.
The optic cups of short-term Tamoxifen users (≤2 years) were found to be significantly smaller in both the lateral and axial directions than the optic cups of age-matched female control subjects, in a study of women who had been selected for the absence of any overt eye disease.[55] This result was consistent with the possibility that Tamoxifen often causes a subclinical degree of swelling at the optic cup, particularly since Tamoxifen blocks swelling-activated chloride channels[50], such as those in astrocytes, and astrocytes are the predominant glial cell in the cup.[56]
OCT and Pattern Visual Evoked Potential monitoring may be therefore needed to adequately observe for subclinical changes in optic nerve head parameters and visual function among Tamoxifen users.[57]

Tamoxifen Keratopathy

Small doses of Tamoxifen can cause clinically significant and visible corneal deposits, in the form of subepithelial deposits, whorls and linear opacities, in approximately 11% of cases.[21] These corneal subepithelial deposits also produce a reversible vortex keratopathy, which is reported to disappear after drug cessation.[58] While using also in vivo confocal microscopy, that is a noninvasive method to examine the cornea at the cellular level[59], corneal depositions were recently reported in 72% of patients receiving Tamoxifen at a dosage of 20 mg/day[60], despite the fact that no pathologic alteration of structure was observed with in vivo confocal microscopy at any corneal level in these patients.

The grading system which was originally proposed for amiodarone-induced vortex keratopathy has been used to describe the degree of Tamoxifen deposition in the cornea.[60]

The structure of Tamoxifen is similar to other cationic amphiphilic drugs known to cause drug-induced lipidoses such as retinopathy and keratopathy, including chloroquine, chlorpromazine, thioridazine, and amiodarone hydrochloride.

These systemic medications reach the cornea via the tear film, aqueous humor, and limbal vasculature. The cationic and amphiphilic nature allows them to penetrate lysosomes.[61]

Once within lysosomes, the drugs and their metabolites bind cellular lipids and form complexes leading to accumulations of lysosomal inclusions, observed as corneal depositions, with whorl-like pattern resulting from the centripetal migration of deposit-laden epithelial cells.[62]

Tamoxifen-associated dry eye disease, taking into account the influence of estrogens on ocular surface, is another factor that might affect cornea and vision.[63]

Tamoxifen Retinopathy

Tamoxifen retinopathy is a well-known side effect of Tamoxifen use, with an estimated prevalence of up to 12%.[20]

Despite the fact that retinopathy associated with Tamoxifen use was first described by Kaiser–Kupfer and coworkers in 1978 [23] there are still limitations in our understanding of this condition, including a lack of definite timeline before toxicity occurs and a lack of understanding surrounding its pathophysiology.

For example, a wide range for the time of exposure before development of Tamoxifen-related ocular side effects has been described in the literature, from 3 weeks to 13 years.[22]

Moreover, the pathogenetic mechanisms of Tamoxifen retinopathy are not completely understood yet. A combination of abnormal lipid metabolism, neurotoxicity, Müller cell dysfunction, decreased estrogen concentration and altered blood flow has been proposed to play a role in Tamoxifen-induced ocular toxicity, although the exact mechanisms of disease remain unclear.[22,29] Of note, a high BMI and the presence of hyperlipidemia were significantly associated with Tamoxifen retinopathy findings.[20]

Characteristic findings of Tamoxifen retinopathy include refractile crystalline deposits on fundus evaluation and hyporeflective foveal cavitations and focal disruption of the photoreceptor layer in OCT. [22, 64-65]

The most frequently described funduscopic findings in Tamoxifen retinopathy are reduced foveal reflex, macular pigmentary changes or RPE irregularities, bilateral presence in the inner layers of the retina of crystals or reflective deposits, and macular edema.

Tamoxifen-related crystals have been generally described as multiple, fine, superficial, with white, yellowish or cream-colored appearance; these refractile deposits tend to be more concentrated in, but not limited to, the macula. In fact, peripheral retinal alterations, with peripheral refractile crystals, have rarely been reported in association with Tamoxifen exposure.[66]

Crystal formation mechanism is not defined yet, but neuronal degeneration deriving from toxicity to Müller cells is the most suggested theory.[65]

OCT may show inner and outer retinal changes presenting as hyper-reflective deposits, foveal cavitations, or a combination of both; isolated, outer photoreceptor defects in patients taking oral Tamoxifen have also been described. [20, 40, 67]

Focal photoreceptor disruption involves loss or rarefaction of ellipsoid/interdigitation zone, either in isolation or associated with external limiting membrane or RPE disruption at the foveal level.

Moreover, Tamoxifen has been associated with development of macular holes, and Tamoxifen therapy was found to convey an increased risk of developing a macular hole[68]; macular holes seem to form as the cystic spaces in fovea coalesce and enlarge.[69-70]

Tamoxifen-induced changes in sex steroid homeostasis, taking into account estrogen receptor presence in the human eye[71], may also cause an increase and an exacerbation of vitreo-retinal tractions, affecting macular hole formation.[72]

Therefore, ophthalmologists should be aware of this association given the frequency of Tamoxifen use, as well as the reported low success rate of surgical repair with pars plana vitrectomy.[70]

In addition to morphologic changes of Tamoxifen retinopathy using OCT, vascular changes on OCT-A, such as telangiectatic vascular changes at the deep capillary plexus and right-angled vessels, similar to those observed in the early stages of MacTel 2, have been reported[40].

When evaluating choroidal features Tamoxifen has been reported to affect choroidal thickness[43-44], and pachychoroid-related disorders[73] have been reported in patients treated

with Tamoxifen, such as central serous chorioretinopathy and pachychoroid pigment epitheliopathy. [74-76]

Tamoxifen treatment has been associated with increased serum levels of testosterone, cortisol, and cortisone.[77] Elevated steroid levels are known to affect choroidal vascular permeability and vascular dilatation of choroid vessels, and this may lead to the development of disorders in the pachychoroid spectrum.

When considering functional assessments such as visual acuity, color contrast, visual field, and Electroretinogram (ERG), despite the fact that they might be considered appropriate for assessment and screening of Tamoxifen retinopathy, they have not been found to be effective for screening these patients[22], and tests such as multifocal ERG may not be sufficiently sensitive to detect Tamoxifen-associated changes that might occur in the retina.[78]

Study protocol

This protocol study aimed to evaluate the prevalence and the structural chorioretinal findings of Tamoxifen-related side effects by means of different techniques including fundus evaluation and non-invasive multimodal imaging with OCT and OCT-A.
Patients with breast cancer who had a history of Tamoxifen prescription were evaluated, with additional evaluations according to clinical judgement and in case of ophthalmological disturbances. A complete ophthalmological examination was performed, including measurement of best-corrected visual acuity (BCVA), Goldmann applanation tonometry, slit lamp biomicroscopy, and dilated fundus examination; ophthalmological imaging included chorioretinal multimodal imaging with OCT and OCT-A. Institutional Review Roard and Ethics Committee approval were obtained, and the study complied with the tenets of the Declaration of Helsinki. Informed consent was obtained from all participants.
Exclusion criteria included known prior diagnosis or findings of retinal disease and any disease process associated with chorioretinal changes, glaucoma, ocular hypertension or other optic neuropathies, uveitis, a history of systemic illnesses or medications implicated in chorioretinal alterations and toxicity (including diabetes and arterial hypertension), and a history of ocular surgery. Morover, patients with significant media opacities that precluded fundus imaging were excluded from the study.
In order to avoid confounding factors, patients that were treated with aromatase inhibitors and chemotherapy were excluded from the study. Distant radiotherapy was not considered a confounding variable.
Baseline characteristics, including age, gender, history of chemotherapy, presence of systemic diseases, Tamoxifen daily dose, age at initial Tamoxifen use, duration of Tamoxifen intake, and cumulative dose of Tamoxifen intake were recorded; Body mass index (BMI) was calculated, following the report that a high BMI and the presence of hyperlipidemia were significantly associated with Tamoxifen retinopathy.[20]
Optic nerve and macular spectral domain OCT (SD-OCT) (with radial and raster scans) and OCT-A images were acquired using OCT SPECTRALIS (Heidelberg Engineering, Heidelberg, Germany) after pharmacologic dilation. All scans were acquired between 3 PM and 6 PM in order to limit circadian changes in choroidal thickness. Using an Early Treatment Diagnostic Retinopathy Study (ETDRS) circle at the macular level, the automated retinal segmentation software was applied to determine macular thickness. The mean thickness was measured in all 9 ETDRS grid sectors, which consisted of two concentric circles of 3-mm and 6-mm diameters surrounding the central foveal area (1 mm) divided into quadrants.
Choroidal vascularity index (CVI) was assessed below the central foveal region on SD-OCT, while vessel density (VD) and vessel length density (VLD) from OCT-A scans, as described in previous studies; ImageJ (National Institutes of Health, Bethesda, MD) was used to binarize the images and calculate VD and VLD in accordance with previously published techniques.[79-83]
All scans of both eyes were systematically examined for alterations by two independent observers; in case of disagreement between the two ophthalmologists, another physician was consulted to obtain an acceptable interpretation of the disputed image.
When performing statistical analysis qualitative variables were expressed as frequencies and percentages; quantitative variables were expressed using mean and standard deviation (SD). Student's t-test was used to compare continuous variables; chi-squared test was used to compare categorical variables. A p value ≤ 0.05 was considered statistically significant.

Results

Among 133 patients who were examined at the Eye Clinic of Polytechnic University of Marche, Ancona, Italy, 62 were excluded after meeting exclusion criteria; a total of 71 patients were included in the analysis.

All patients minus two were women (97.2%), with a mean patient age of 50.9 years (SD 6.1 years) and a mean BMI of 23.7 (SD 3.3); they were administered Tamoxifen (20 mg) daily for adjuvant endocrine therapy after breast cancer surgery. The mean duration of Tamoxifen therapy was 21.5 months (SD 21.6 months), while mean cumulative dose of Tamoxifen intake was 13334.4 mg (SD 13371.2 mg); all subjects had a best-corrected visual acuity (BCVA) of 20/25 or better. Thirty-seven patients (52.1%) had been treated for a period ≤12 months, 9 additional patients (64.8%) for a period≤24 months.

Using the ETDRS grid, mean macular thickness was 313±30 μm, mean central foveal subfield thickness was 280±23 μm, mean inner 3-mm subfield thickness was 341±15 μm and mean outer 6-mm subfield thickness was 294±19 μm.

Twenty-one patients (29.6%) showed features of Tamoxifen retinopathy; of those, 13 patients (18.3%) showed alterations in both eyes, while 8 patients (11.3%) had unilateral alterations. Regarding Tamoxifen retinopathy features, one patient showed multiple, fine, superficial crystals in the macula of both eyes, while all the other patients presented alterations at the level of ellipsoid and interdigitation zone, either in isolation or associated with external limiting membrane disruption at the foveal level, on one or both eyes. No patients showed intraretinal cavitations or macular holes.

The differences in age, BMI, duration of treatment and cumulative Tamoxifen dose between the groups of patients without and with Tamoxifen retinopathy were not statistically significant (p=0.983, p=0.601, p=0.442, p=0.442, respectively); no statistical significance was found when evaluating separately the patients with unilateral and bilateral retinopathy.

Patients' features are summarised in Tables 1 and 2.

Given that a high BMI was associated with Tamoxifen retinopathy findings[20], a statistical analysis was performed on the 25 patients (35.2%) with BMI ≥25 (overweight and obese patients), without findings of statistical correlation and significant association between Tamoxifen retinopathy and BMI (no retinopathy patients N=19; patients with retinopathy N=6; p=0.448).

In order to evaluate whether significant associations were present between Tamoxifen retinopathy findings and increasing cumulative doses, the 35 patients (49.3%) that had received more than 7440 mg of Tamoxifen (median Tamoxifen cumulative dose) were analyzed, without findings of statistical correlation between these two variables (no retinopathy patients N=23; patients with retinopathy N=12; p=0.391).

When evaluating OCT-A images, vascular changes such as telangiectatic vascular changes at the deep capillary plexus and right-angled vessels, that have been reported to occur in Tamoxifen retinopathy[40], were not present in the evaluated patients.

The average CVI was found to be 61.76 ± 5.23% in these patients; superficial, intermediate, deep capillary plexuses macular vascular densities were 68.68 ± 6.61%, 79.82 ± 5.17%, and 76.85 ± 5.46%, respectively, while choriocapillaris vascular density was 62.89 ± 6.98%.

Vessel length density was 10.39 ± 2.57 mm^{-1}, 6.68 ± 1.72 mm^{-1}, 7.50 ± 2.00 mm^{-1} and 11.00 ± 2.55 mm^{-1} for superficial, intermediate, deep capillary plexuses and choriocapillaris, respectively.

When evaluating separately the patients with and without retinopathy a statistically significant difference was found in terms of ICP VD (retinopathy patients mean 81.03 ± 4.07%; no retinopathy patients mean 79.11 ± 5.62%; p=0.040), DCP VD (retinopathy patients mean

78.35 ± 4.66%; no retinopathy patients mean 75.97 ± 5.72%; p=0.015) and CVI (retinopathy patients mean 60.04 ± 5.22%; no retinopathy patients mean 62.45 ± 5.22%; p=0.005).
Given that this study did not evaluate healthy age-matched individuals no other comparisons could be performed in terms of CVI, VD and VLD.
While evaluating cornea, one patient (presenting also features of Tamoxifen retinopathy) showed bilateral verticillate whorl-like pattern.
Three patients (4.2%) showed unilateral microvascular abnormalities in the retinal periphery, that were also evaluated by means of fluorescein angiography, while two patients presented peripheral retinal breaks that were treated by means of laser photocoagulation.

Discussion

Tamoxifen-related ocular side effects have been described in up to 12% of the treated patients[20], with OCT allowing to evaluate early and subtle changes in retinal and choroidal architecture. In past studies, without the use of OCT imaging, cases of intraretinal cavitations and retinal abnormalities without crystalline deposits on fundus examination might have been missed, resulting in an underestimation of Tamoxifen retinopathy prevalence.
This study found a higher prevalence of Tamoxifen-related alterations than previously reported in the literature; in fact, 21 patients (29.6%) showed features of Tamoxifen retinopathy, with 13 patients (18.3%) showing OCT alterations in both eyes.
Just one patient showed multiple, fine, superficial crystals in the macula of both eyes on fundus evaluation (Figure 1), while all the other patients presented OCT alterations at the level of ellipsoid and interdigitation zone, either in isolation or associated with external limiting membrane disruption at the foveal level, in one or both eyes (Figures 2 and 3).
No evaluated patients showed intraretinal cavitations or macular holes, and this could be due to the fact that many patients had been treated with Tamoxifen for relatively short periods of time, while Tamoxifen-related macular hole case reports in the current literature seem to be associated with higher cumulative doses and longer periods of treatment[70, 84].
All the OCT-identified structural findings may represent an early indicator of retinal toxicity in patients undergoing Tamoxifen therapy and should be therefore carefully evaluated in the follow-up period. Because of this, after discussion with their oncologist, no patients discontinued therapy after finding Tamoxifen-induced ocular alterations, having been suggested to receive additional ophthalmological evaluations, including OCT, once every 6 months.
No statistical differences were found in terms of age, BMI, duration of treatment and cumulative Tamoxifen dose between the groups of patients without and with Tamoxifen retinopathy.
Given that a high BMI was associated with Tamoxifen retinopathy findings[20], it was evaluated whether significant associations between Tamoxifen retinopathy and BMI could be found, but the results did not reach statistical significance.
Similar results could be reported during evaluation whether significant associations were present between Tamoxifen retinopathy findings and increasing cumulative doses.
It is noteworthy that using the ETDRS grid mean macular thickness, mean central foveal subfield thickness, mean inner 3-mm subfield thickness and mean outer 6-mm subfield thickness values were reported for the first time in this particular group of patients.
As chemotherapy has been associated with retinal toxicity [85], patients that had been previously treated with chemotherapy were excluded from the study; moreover, in order to avoid confounding factors, so were the patients with an history of use of aromatase inhibitors, that were found to be more effective than Tamoxifen in reducing breast cancer mortality in postmenopausal women [86] but are not without possible ocular side effects. [45]
As no reports were found on retinal toxicity associated with distant radiotherapy, it was not considered a possible confounding variable while assessing the presence of Tamoxifen-induced ocular alterations.
When evaluating OCT-A images, vascular changes such as telangiectatic vascular changes at the deep capillary plexus and right-angled vessels, that have been previously reported as a finding in Tamoxifen retinopathy [40], were not present in the evaluated patients.
However, after separate evaluation of the patients with and without retinopathy, a statistically significant difference was found in terms of ICP VD, DCP VD and CVI; these

findings could be added to the currently limited literature on vascular alterations in Tamoxifen retinopathy [40,44,87].
Given that this study did not evaluate healthy age-matched individuals, no other comparisons could be performed in terms of CVI, VD and VLD.
However, data for these vascular parameters in adults treated with Tamoxifen and assessed by means of OCT-A were provided; after using OCT-A in healthy subjects it would be possible to draw comparisons in terms of density of the macular vascular networks.
Although diurnal variation in choroidal thickness was considered, and all OCT scans were acquired in the afternoon in order to limit circadian changes in choroidal thickness, other influencing factors that could represent confounding factors might not have been taken into consideration.
Despite not having been properly evaluated during the study, many patients complained of symptoms related to dry eye disease, especially those who had recently started Tamoxifen treatment; this topic may represent the focus of future investigations, given the influence of estrogens on ocular surface.[63]
As previously said, after discussion with their oncologist, no patients discontinued therapy after finding Tamoxifen-induced ocular alterations, having been suggested to receive additional ophthalmological evaluations, including OCT, once every 6 months.
Despite the fact that some Authors recommend screening be performed every 6 months after patients have been on 20 mg Tamoxifen daily therapy for 2 years [29], patients with low cumulative doses were evaluated as well in this study (46 patients had been treated for less than 24 months, and 37 for less than a year), and this may help in establishing a dose dependency statement in the future.[44]
Moreover, given that the earliest toxicity reported in the literature occurred after only 3 weeks of Tamoxifen initiation[74], an evaluation that establishes baseline ocular features might be really important in these patients.
Since functional assessments have not been found to be effective for screening Tamoxifen patients [22], funduscopy and OCT seem to be the most useful exams to be performed during ophthalmological evaluation.
It must be acknowledged that this study has several limitations, such as the lack of a control group that precludes additional discussion on some of the findings; however, it represents a study that through use of multimodal imaging further characterises Tamoxifen-associated eye disease in breast cancer patients, excluding many confounding factors, detailing a higher prevalence of Tamoxifen-related alterations than previously reported in the literature.
Additional studies, including a detailed follow-up of these patients, are warranted to confirm these preliminary results and to provide further insight into this topic.

Conclusions

This study found a much higher prevalence of Tamoxifen-related alterations than previously reported in the literature; in fact, 29.6% of the patients showed features of Tamoxifen retinopathy. Only a small percentage of breast cancer patients experienced clinically evident ocular side effects from their medication; the use of non-invasive instruments such as OCT and OCT-A allowed to report early and subtle changes in retinal architecture, providing detailed visualization of the tissues and of the vascular networks in the eye.
The presence of subclinical structural chorioretinal findings related to Tamoxifen intake should be further studied and could give important clues regarding the pathophysiology and early recognition of Tamoxifen toxicity.
Analysis of intervals between drug initiation and findings suggesting ocular toxicity may provide more information about the optimal screening periods.
There is a need for a detailed ophthalmological evaluation, including OCT, in patients before and after starting Tamoxifen therapy, followed by clear instructions to report even subtle visual symptoms. Establishing baseline ocular features is mandatory, at least yearly evaluations seem to be in order as the reported ocular alterations in this study were found in asymptomatic patients. More closely monitoring should be recommended if ocular alterations are observed, and this is particularly important in patients with hyperlipidemia and elevated BMI since an association between these comorbidities and Tamoxifen retinopathy was reported in the literature.
Any sign of symptomatic or asymptomatic ocular conditions should prompt a discussion with the patient as well as the oncologist.
OCT provides valuable information for identifying structural changes and evaluating ocular alterations in patients receiving Tamoxifen therapy.
The synergistic eye toxicity of aromatase inhibitors and chemotherapy might be the focus of future studies.
It is hoped that these findings may provide further insight and help medical decision-making in patients receiving Tamoxifen therapy for breast cancer.

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Table 1. Patients' features in terms of sex, age, BMI, duration of treatment and cumulative Tamoxifen dose.

	Total	No retinopathy	Retinopathy	p
	N=71	N=50	N=21	
Sex, F, n (%)	69(97.2%)	48(96.0%)	21(100%)	0.353
Age (years), mean±sd	50.9±6.1	50.9±5.9	50.9±6.8	0.983
Weight (Kg), mean±sd	64.0±9.8	64.7±9.6	62.4±10.3	0.363
Height (m), mean±sd	1.64±0.06	1.65±0.06	1.63±0.05	0.230
BMI, mean±sd	23.7±3.3	23.9±3.5	23.4±2.8	0.601
Duration of Tamoxifen intake (months), mean±sd	21.5±21.6	20.2±21.2	24.6±22.6	0.442
Tamoxifen Dose (mg), mean±sd	13334.4±13371.2	12536.4±13158.3	15234.3±14006.5	0.442

Table 2. Separate evaluation of the patients with unilateral and bilateral retinopathy.

	Total	No retinopathy	Unilateral Retinopathy	Bilateral Retinopathy	p
	N=71	N=50	N=8	N=13	
Sex, F, n (%)	69(97.2%)	48(96.0%)	8(100%)	13(100%)	0.649
Age (years), mean±sd	50.9±6.1	50.9±5.9	49.1±5.8	52.0±7.3	0.585
Weight (Kg), mean±sd	64.0±9.8	64.7±9.6	65.3±12.0	60.6±9.3	0.384
Height (m), mean±sd	1.64±0.06	1.65±0.06	1.64±0.06	1.62±0.04	0.385
BMI, mean±sd	23.7±3.3	23.9±3.5	24.1±2.9	23.0±2.8	0.658
Duration of Tamoxifen intake (months), mean±sd	21.5±21.6	20.2±21.2	22.5±26.0	25.8±21.3	0.703
Tamoxifen Dose (mg), mean±sd	13334.4±13371.2	12536.4±13158.3	13950.0±16096.14	16024.6±13193.2	0.703

Figure 1. Multimodal imaging scans (retinography, infrared imaging, OCT) of a female patient showing multiple, fine, superficial crystals in the macula of both eyes on fundus evaluation.

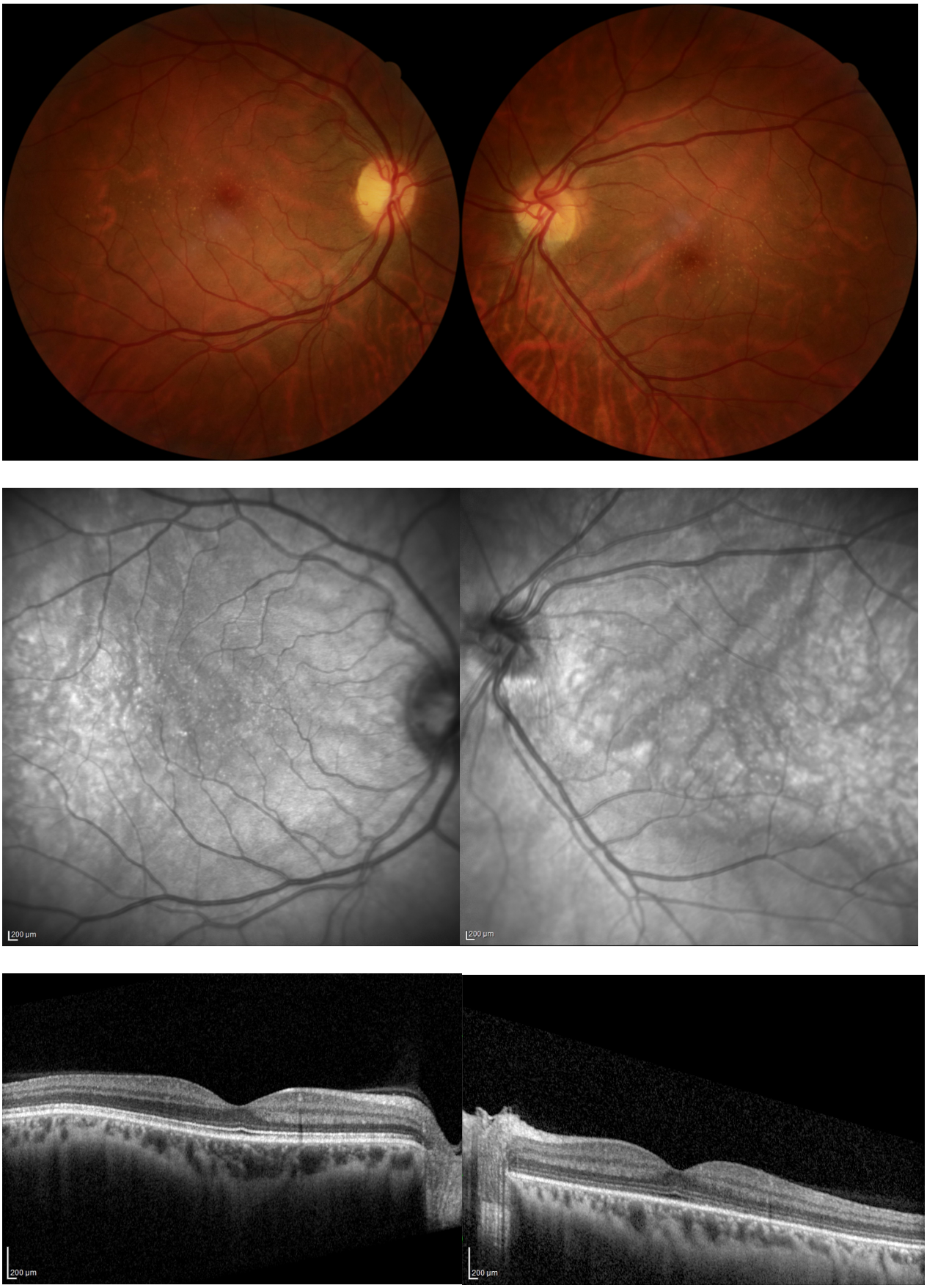

Figure 2. Spectral-domain OCT scans of a female patient showing bilateral foveal disruption of external limiting membrane and alterations at the level of ellipsoid zone.

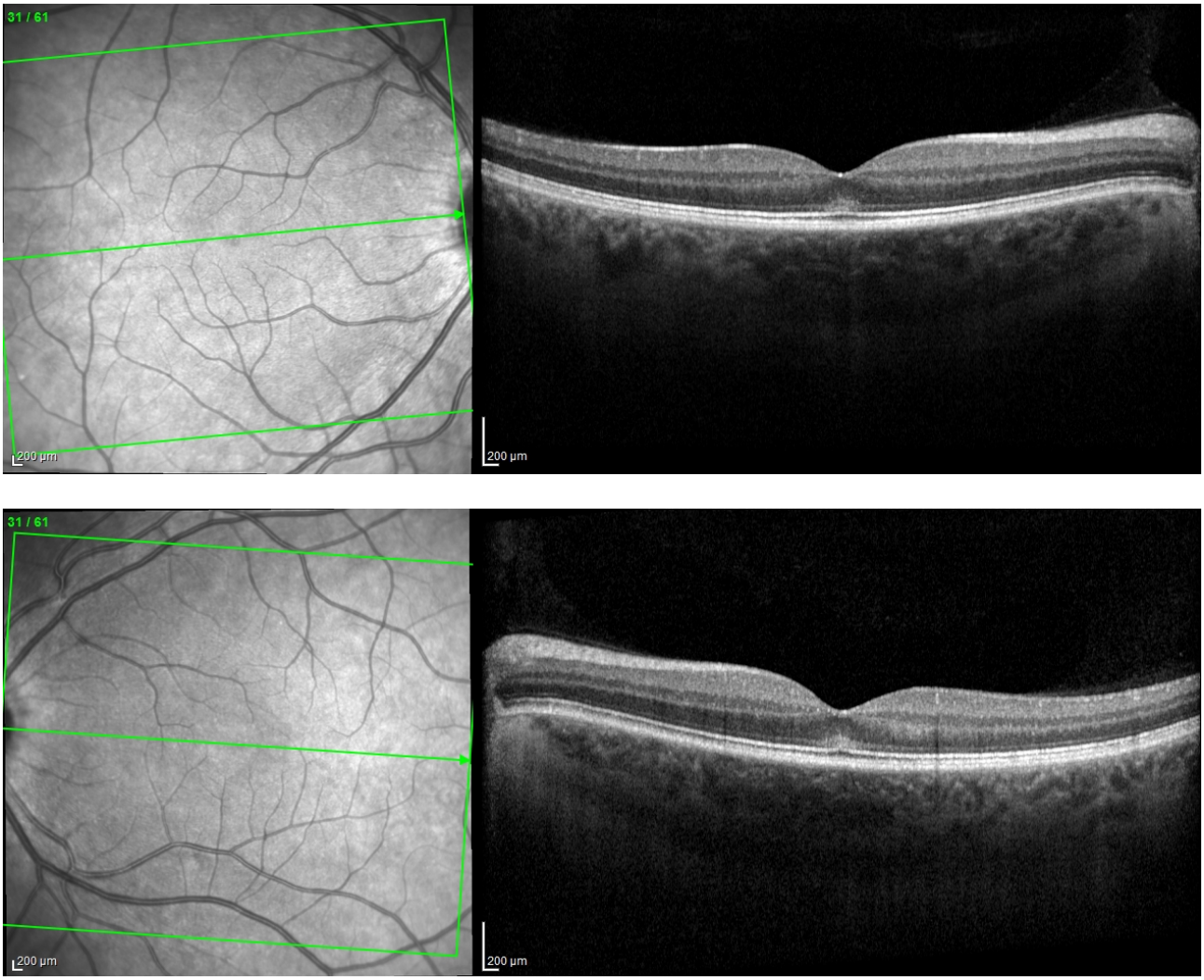

Figure 3. Spectral-domain OCT scans of a female patient showing subtle bilateral foveal alterations at the level of ellipsoid and interdigitation zone.