Title: Can Low Dose Radiation Therapy (2 × 2 Gy) be Used in Primary Bilateral Conjunctival Follicular Lymphoma?

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Can low-dose radiation therapy (2x2 Gy) be used in primary bilateral conjunctival follicular lymphoma?

Kommt eine niedrig dosierte Radiotherapie (2x2 Gy) bei primären bilateralen folliculären Bindehaut-Lymphom infrage?

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Introduction

In 2013, the Stanford Group suggested a low-dose radiation therapy (2x2 Gy) for orbital non-Hodgkin lymphoma (NHL), having observed no in-treatment field relapses in 27 treated sites (clinical stage IE-IV), with a complete response (CR) in 23 sites, a partial response (PR) in 3 sites, and steady disease (SD) in 1 site, after a median follow-up of 26 months [1]. We applied this protocol in a case of bilateral conjunctival follicular lymphoma grade I-II.

Case Report

A 59-year-old female artistic painter presented with tearing, itchy eyes and a bilateral follicular tarsal conjunctivitis, which was initially presumed to be allergic (Fig. 1). When neither anti-histaminic (topical and systemic), nor topical steroid therapy had any significant effect, a Chlamydia PCR analysis was performed, with twice a negative result. Patient was then lost to follow-up.

Four years after her initial presentation, the patient saw her local ophthalmologist, who did a biopsy of this chronic follicular conjunctivitis, revealing the diagnosis of a follicular lymphoma grade I-II, BCL2+ (Fig. 2).

A general check-up, including also a total body Computed Tomography (CT)-scan and a bone marrow biopsy, was performed and resulted negative, as was the patient’s HIV and Hepatitis B and C serology. Referring to the Stanford paper [1], our radiation oncologist proposed a low-dose radiation therapy (LDRT) (2x2 Gy) for this low-grade non-Hodgkin lymphoma of the ocular adnexa, our patient being extremely pre-occupied because of the potential radiation induced side-effects reportedly related to conventional doses at about 30 Gy. Three months following this low-dose photon therapy (2x2 Gy) of both conjunctivas, the tarsal follicles had clearly regressed (Fig. 3A and B). At six months the response was still incomplete and at nine months an in-treatment field relapse was observed, most clearly at the left inferior tarsal conjunctiva (Fig. 3C), and presumably also at the right superior tarsal conjunctiva. An orbital magnetic resonance imaging (MRI) did not reveal any visible orbital lymphomatous infiltration.

Consequently, a second external beam radiation therapy was performed, delivering 14x1.8Gy to both orbits, resulting at both conjunctivas in a total cumulative dose of 29.2 Gy, including the 4 Gy of the first radiation therapy.

Three months after the second irradiation, the tarsal follicles had regressed, with a less ‘fleshy’ appearance and a residual reticular scarring of the tarsal conjunctivas (Fig. 3D). Subjectively, the patient
reported less tearing eyes without any significant short-term side effects of the orbital radiation therapy at conventional doses.

**Discussion**

We report a rare case of chronic bilateral conjunctival, follicular non-Hodgkin lymphoma that presented an in-treatment field relapse, nine months after external beam low dose (2x2 Gy) radiation therapy. Though lymphomas represent the most frequent malignant tumors of the ocular adnexa, they remain relatively rare, accounting for 8% of extra-nodal lymphomas. The majority of cases are primary extra-nodal non-Hodgkin B-cell lymphomas and only a minority is secondary to disseminated lymphomas [2, 3]. The most common subtype in the conjunctiva is low-grade extranodal marginal zone lymphoma (EMZL) (81%), with follicular lymphoma (FL) coming second (8%), followed by high-grade diffuse large B-cell lymphoma (3%) and finally, mantle cell lymphoma (3%) [4]. One could speculate that the pathogenesis and bilateral presentation [4] of this rare subtype of conjunctival lymphoma might be related to our patient’s chronic exposure to paint. The pathogenesis of chronic antigenic stimulation has already been reported in cases of EMZL [2, 3, 4], the neoplasia being preceded by a benign chronic inflammation, related to organisms such as Helicobacter pylori, Chlamydia psittaci and hepatitis C [4]. A delay in diagnosis is not unusual [2, 4], because these low-grade conjunctival lymphomas do not provoke a lot of symptoms, as illustrated by our patient who attributed her teary and itching eyes to her occupation as an artistic painter.

Conjunctival lymphomas being so rare, therapeutic recommendations are only based on retrospective case series [2]. For localized low-grade diffuse follicular lymphoma most papers recommend fractionated external beam radiation therapy at an average dose of 30 Gy, with reported local control rates up to 100% [2, 5]. Short term side effects include moderate cutaneous or conjunctival inflammation, while the most frequent long-term complications consist of dry eye syndrome and cataract. Though severe late manifestations such as corneal ulceration, ischemic retinopathy and neuropathy, orbital fat-tissue reduction and even neovascular glaucoma should not occur at doses less than 35 Gy [5], our patient was extremely concerned about this risk. Because of the lack of in-treatment field relapses in the case series reported by Fasola et al., including 55% of follicular lymphomas [1], we proposed their protocol for the first time in this lady. After an initial partial response, our patient presented a bilateral in-treatment field
relapse after only nine months. Though low dose irradiation can indeed be a palliative option in patients with advanced stage of non-Hodgkin lymphoma and involvement of the ocular adnexae, our case incites to caution in applying this protocol in localized primary orbital lymphoma cases, as the risk of systemic disease has been reported as high as 21%, without any knowledge about when dissemination occurs [4].
References


Figure Legends

Fig 1. Initial slit lamp photos, illustrating bilateral (A: RE and B: LE) inferior tarsal follicles, more pronounced at the LE, that at that time were diagnosed as allergic conjunctivitis.

Fig 2. Histopathologic pictures following incisional conjunctival biopsy, four years later, leading to the diagnosis of conjunctival follicular lymphoma. Presence of a dense lymphoid infiltrate consisting mainly of small cells with angulated nuclei, but also intermediate sized cells showing nuclei with mottled chromatine (A: HE 63x and B: HE 252x). Immunohistochemistry reveals a majority of B-cell lymphocytes CD20+ (C) and CD79a+, with a minority of CD3+ small reactive T-cells, mainly located at the periphery of the B-cell lymphoid infiltrate (D). Most lymphoid cells are positive for BCL6 (E), while CD21 (F) leads to a dendritic staining at the base of the lymphoid infiltrate.

Fig 3. Clinical evolution of the conjunctival follicular lymphoma at the left lower eyelid in response to radiation therapy. A. Presentation before treatment. B. Partial regression three months after low dose (2x2Gy) conjunctival radiation therapy. C. In treatment field relapse (black arrow head) nine months after treatment. D. Follicular regression three months after a second orbital radiation therapy at conventional doses, leaving behind a honeycomb patterned interseptal fibrosis.