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Lazarevic, Diana ; Ramelyte, Egle ; Dummer, Reinhard ; Imhof, Laurence

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Radiotherapy in Periocular Cutaneous Malignancies: A Retrospective Study

Diana Lazarevic Egle Ramelyte Reinhard Dummer Laurence Imhof

Department of Dermatology, University Hospital Zurich, Zurich, Switzerland

Keywords
Periocular skin malignancies · Radiotherapy · Recurrence rate

Abstract
Background: Due to the importance of function and cosmetics, periocular skin malignancies represent a therapeutic challenge. ***Objective:*** To evaluate the safety and efficacy of radiotherapy (RT) treating periocular skin tumors. ***Methods:*** Data of patients with periocular tumors treated with grenz or soft X-rays at the University Hospital Zurich, Switzerland, between 2009 and 2014 were reviewed. Basal cell carcinoma (BCC) and squamous cell carcinoma (SCC) with associated in situ lesions, cutaneous melanoma, lentigo maligna (LM), cutaneous lymphoma and Kaposi's sarcoma were included in the analysis. ***Results:*** We found 159 periocular lesions in 145 patients. Overall recurrence was highest for actinic keratosis and Bowen's disease (27%), melanoma (17%) and LM (15%), whereas SCC and BCC showed recurrence in 11 and 10%, respectively. 45% of all recurrences occurred within 12 months after treatment, with a median time to recurrence of 13 months (range 3–73). ***Conclusion:*** RT, which provides a good therapeutic response with minimal adverse events, is a therapy option for periocular cutaneous malignancies.

Introduction

Up to 10% of all skin malignancies occur in the periocular region [1]. Basal cell carcinoma (BCC) is the most common malignant eyelid tumor followed by squamous cell carcinoma (SCC), sebaceous cell carcinoma, Merkel cell carcinoma, cutaneous melanoma and other rare tumors [1–3]. Likewise, in situ lesions, such as actinic keratosis (AK) and Bowen's disease (BD), can affect the periocular skin [2, 3]. Although the majority of cutaneous neoplasms can be treated by excision [4–9], excessive surgical intervention in the periocular site may lead to anatomical dysfunction and poor aesthetic outcome [10–12]. Less invasive approaches, such as photodynamic therapy or cryotherapy, represent a treatment option for superficial cutaneous neoplasms [7–9]. However, limited penetration restricts their applicability in invasive tumors. Radiotherapy (RT) with external beam radiation (using photons or electrons) and brachytherapy (radionuclide-based or electronic) is an attractive treatment option for cutaneous tumors either as primary modality or adjunct to surgery [5–8, 13]. It has previously been reported that RT with grenz and soft X-rays is effective in cutaneous malignancies [14, 15], yet data on efficacy in the periocular area are still scarce. The aim of this retrospective study was to evaluate safety, cosmetic outcome, response to and recurrence rate after RT of periocular skin tumors.

E-Mail karger@karger.com
www.karger.com/drm

Laurence Imhof, MD
Department of Dermatology
University Hospital Zurich
Gloriastrasse 31, CH–8091 Zurich (Switzerland)
E-Mail laurence.imhof@usz.ch

Patients and Methods

For further details, see the online supplementary material (see www.karger.com/doi/10.1159/000496539 for all online suppl. material) [16–18] (Fig. 1).

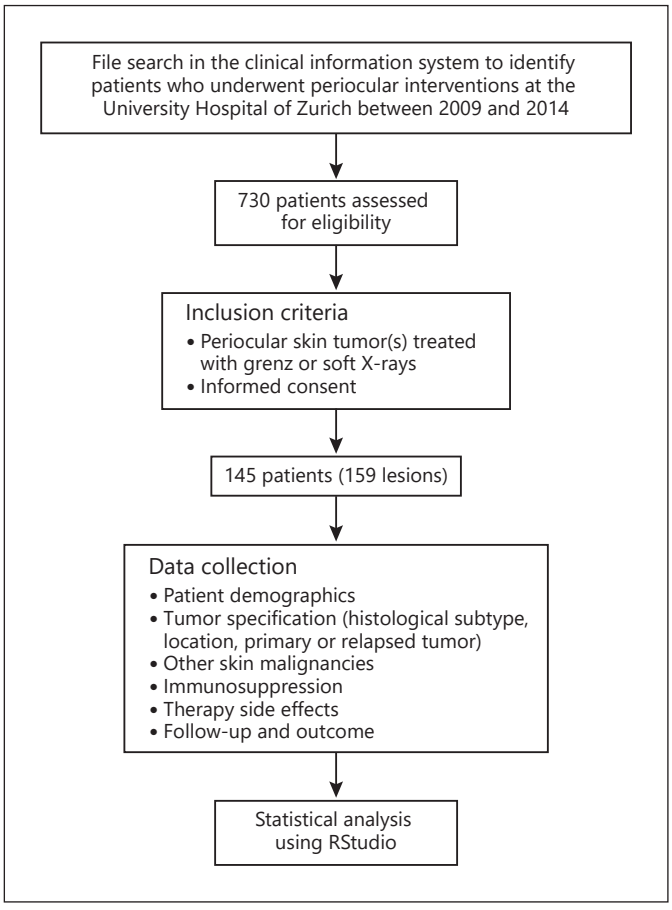

Fig. 1. Flowchart of Patients and Methods.

Results

In 145 patients, a total of 159 lesions were treated. The mean age at therapy start was 76 years (SD ±10.3) and the study cohort consisted of 86 females (54%) and 73 (46%) males. Nearly half of the treated lesions were BCCs (n = 69, 43%), followed by lentigo maligna (LM) (n = 27, 17%), SCC and cutaneous melanoma (each n = 18, 11%), AK/BD (n = 15, 9%) and cutaneous lymphoma/Kaposi's sarcoma (n = 12, 8%) (see online suppl. Table 1). In 10% of the patients, 2 or 3 periocular lesions were simultaneously treated with RT. The distribution pattern of the lesions is shown in Figure 2. In 75% of the cases, RT was the 1st-line therapy, the rest was pretreated with surgery (16%) or conservative therapy (1% imiquimod in LM lesions or 4% PUVA therapy in mycosis fungoides patients). 38 patients (26%) were immunocompromised, 5 of whom had more than 1 immunosuppressive disorder: 12 patients had a diabetic disorder, 13 patients were on iatrogenic immunosuppression, while 10 suffered from lymphoma, 9 from solid cancer or hematopoietic induced immunosuppression and 2 from alcohol dependence.

The administered total dose per field ranged from 12 to 120 Gy and was given at 2- to 5-day intervals for 3–13 therapy sessions (fractions). Total dose and fractionation schedules were based on tumor subtype, size and location of the lesion. LM and melanoma lesions were treated with grenz or soft X-rays (10–20 kV), while other lesions were treated with soft rays (20–50 kV). Further details on RT parameters are summarized in online supplementary Table 2. Most frequent irradiation-related toxicity (79%) was radiation dermatitis grade 1 (faint erythema) according to Common Terminology Criteria for Adverse Events (CTCAE 4.03) [16], which did not require any intervention and resolved within 4–6 weeks after the end of therapy. In 27 cases moderate adverse events (grade 2 toxicities, local intervention indicated) including radiation dermatitis (moderate erythema/edema and patchy moist desquamation, n = 21), infection of the wound (n = 2), symptomatic conjunctivitis (n = 2) or blepharitis (n = 1) and canalicular stenosis (n = 1) were documented. No grade 3 toxicities (severe adverse events) occurred under the RT. A patient example of the clinical outcome after irradiation is presented in Figure 3. Patients were reassessed at the Dermatology Department 4 weeks after the end of RT, whereas further oncological follow-up was either continued there (n = 60, 41%) or overtaken by the referring physician (n = 85, 59%). The mean follow-up time was 43 months (SD ±27).

Overall recurrence was 13% (20 out of 159 lesions), with the highest rate for AK/BD (n = 4, 27%), cutaneous melanoma (n = 3, 17%) and LM (n = 4, 15%), followed by SCC and BCC with a recurrence in 11% (n = 2) and 10% (n = 7), respectively. However, 2 SCCs (well- and moderately differentiated subtype) and 1 BCC (nodular subtype) did not respond to RT and were therefore excluded from the progression-free survival analysis. 45% of all recurrences occurred within 12 months after treatment, with a median time to recurrence of 13 months (range 3–73 months). Relapse-free survival depending on diagnosis is presented in Figure 4.

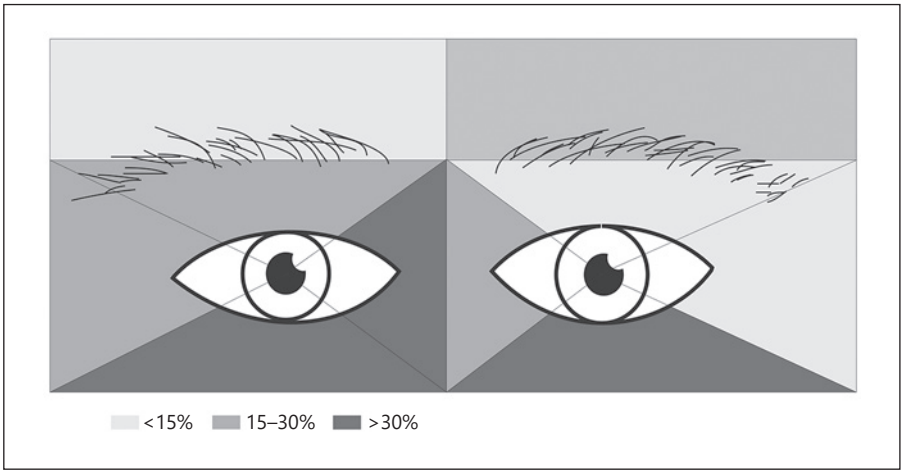

Fig. 2. Distribution of periocular tumors by zone in the treatment population (cumulative view).

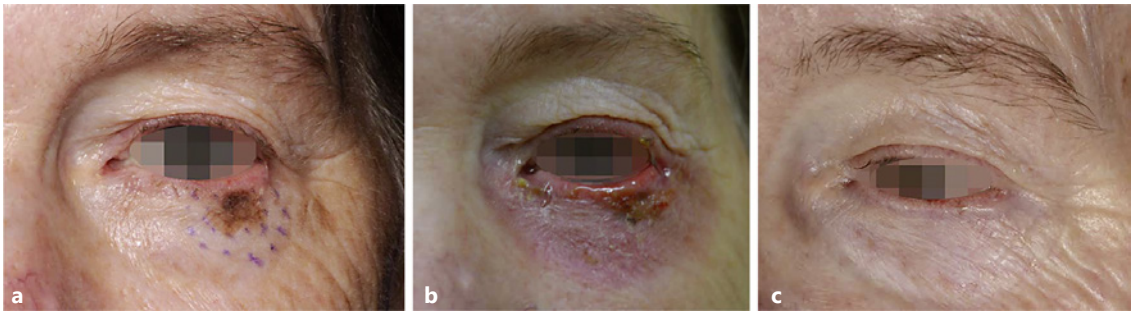

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Fig. 3. Clinical presentation and response to RT. LM lesion on the left lower eyelid in a 79-year-old woman. **a** Before treatment. **b** Local reaction after therapy with soft X-rays (20 kV, 6 Gy × 9 sessions, total 54 Gy). **c** 48 months after treatment.

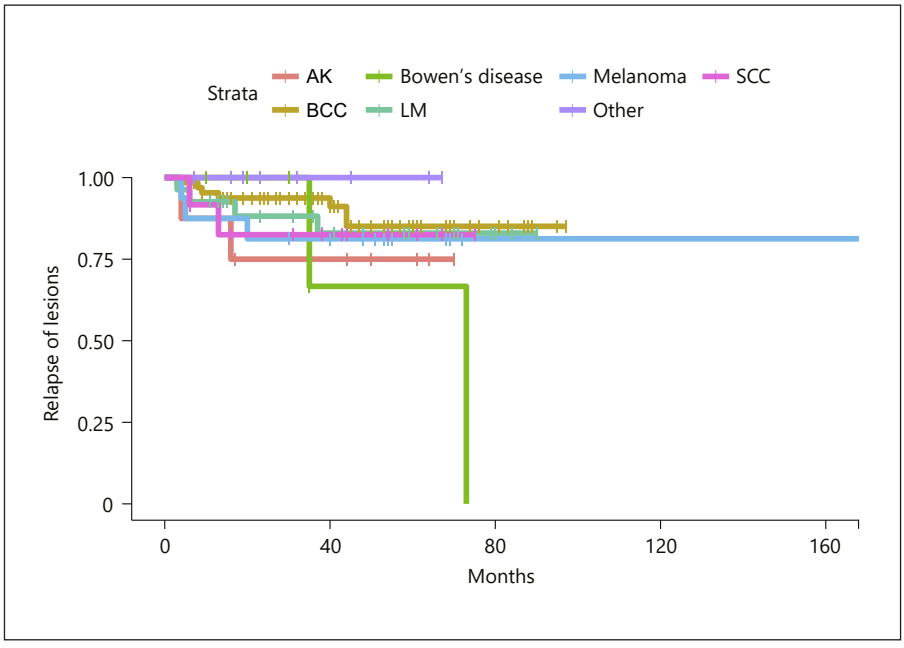

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Fig. 4. Relapse-free survival depending on diagnosis (Kaplan-Meier analysis). AK, actinic keratosis; BCC, basal cell carcinoma; LM, lentigo maligna; SCC, squamous cell carcinoma; other, cutaneous lymphoma (mycosis fungoides, primary cutaneous T-cell lymphoma, diffuse large B-cell lymphoma) and Kaposi's sarcoma.

Discussion

Due to the importance of maintaining functionality and aesthetics, there is a need for subtle yet effective strategies for treating periocular skin tumors. We retrospectively evaluated the efficacy of RT with grenz and soft X-rays in a large cohort of 145 patients with periocular skin neoplasms. As 2/3 of patients showed multiple malignant lesions and 18 patients developed a recurrence of 20 treated lesions, regular clinical examination in patients with a history of cutaneous malignancies is essential even after a successful treatment.

The periocular region can be affected by various benign and (pre-)malignant tumors. Besides BCC, the most frequent malignant tumor, SCC, Merkel cell carcinoma, cutaneous melanoma, as well as in situ lesions and rare tumors can occur in this area, accounting for a total of 5–10% of all cutaneous malignancies [1–3]. Not only may periocular tumors behave more aggressively and show higher recurrence rates, but they also represent a challenge for treatment compared to cutaneous lesions at other sites [10, 12, 19]. Previous data show that periocular neoplasms most frequently occur on the lower eyelid and the medial canthus [1, 2, 20–22], which are surgically challenging areas, carrying a risk of functional and aesthetic complications [10, 12, 19]. Moreover, as observed in our cohort too, periocular tumors tend to develop in fair-skin patients over 60 years of age, who have a history of significant sun exposure [20, 22] – all factors which are known to be associated with the development of skin cancer at any site [23–25], hence concomitant skin cancer is not rare. Among the therapy options for periocular malignancies, such as surgery, RT, cryotherapy, topical immunomodulatory drugs and photodynamic therapy, Mohs' micrographic surgery or intraoperative frozen section is the mainstay of treatment for invasive tumors [4–9, 21]. The 5-year recurrence of periocular skin tumors after Mohs' micrographic surgery is reported to be 2.0% in BCC [21] and 3.6% in SCC [20].

Irradiation is an attractive alternative where surgical excision may lead to anatomical dysfunction and poor aesthetic outcome, multiple lesions have to be treated simultaneously or as follow-up treatment after incomplete surgical excision [7, 8, 26–28]. Treatment with RT induces nonrepairable DNA damage [29], and it has recently been reported to stimulate the activation of immune system pathways [30, 31]. There are different modalities to treat a tumor by RT, and the suitable RT technique should be chosen for each patient individually. Depending on the clinical presentation, low-energy X-rays that penetrate only superficially, brachytherapy (for curved surfaces) or high-energy RT (photons or electrons) are used. The latter penetrates deeper tissues with relative skin sparing. However, when treating cutaneous lesions, deep beam penetration and skin sparing are usually not desirable. The delivery of low-energy kilovoltage photons by a superficial/orthovoltage machine is preferable. In Switzerland specifically for the radiation of the skin, trained dermatologists are allowed to perform superficial X-ray therapy independently of radiation oncologists. Accordingly, we used grenz and soft X-rays in our cohort. These very-low- to low-energy X-rays are directed from outside the body into the tumor and affect the epidermis and dermis while largely sparing deeper tissue [32]. In brachytherapy, however, a sealed radiation source is placed at the tumor site (either inside or next to the tumor tissue) [33]. Previous reviews systematically evaluated the outcome of brachytherapy and superficial RT in periocular skin tumors [27, 34]. A review article on brachytherapy in non-melanoma skin cancer of the eyelid concluded that brachytherapy provides high clinical efficacy (median local control rate 95.2%) and good functional-cosmetic outcome (median 100%) [34]. In addition, especially in old and frail patients, brachytherapy is a safe treatment modality [35].

Farshad et al. [15] analyzed patients with LM and LM melanoma treated with grenz or soft X-rays. The overall recurrence was 7% and the mean time to recurrence 45.6 months. Interestingly, all of the recurrent lesions were located on the face. Another study on LM and early LM melanoma by Hedblad and Mallbris [36] evaluated the efficacy of grenz rays and reported a residual lesion in 15 and recurrence in 58 out of 593 lesions, 73% of which relapsed within 24 months after the end of treatment. This is consistent with our data (70% of recurrences within 24 months, however in our cohort a smaller percentage in the group of melanocytic lesions) and emphasizes the importance of follow-up for at least 2 years after the end of treatment.

The reported overall recurrence at 5 years after the RT is 13.8% in SCC [14] and 15.8% in BCC [37]. As far as the periocular localization is concerned, Fitzpatrick et al. [38] reported a 5-year tumor control rate of 95% for BCC and 93.3% for SCC. In our cohort we found a recurrence rate of 6% after 1 year and 9% after 2 years in 112 patients, who were followed up for at least 24 months. Overall recurrence in BCC was 10% ($n = 7$), in SCC 11% ($n = 2$), in LM 15% ($n = 4$), in cutaneous melanoma 17% ($n = 3$) and in AK/BD 27% ($n = 4$), with a median time to recurrence of 13 months (range 3–73). Interestingly as melanocytic

neoplasms were the first to recur, all of the recurred SCC and AK have done so within 16 months after the end of RT. However, time to recurrence must be evaluated cautiously as it is highly dependent on the follow-up time points. In periocular AK, previous studies on efficacy of topical 5% fluorouracil reported a recurrence rate of 23% with a median time to recurrence of 12 months (range 6–19 months) [39], while another study used 3% diclofenac gel at periocular sites and showed recurrence of 50% [40], with both therapies demonstrating results by far worse than those seen in RT.

In our analyses we could not find any factor for a higher risk of recurrence. Location of the lesion ($p = 0.1572$), irradiation field size ($p = 0.189$), if the lesion was recurrent at therapy start ($p = 0.08787$) or subtypes in BCCs ($p = 0.5026$) and differentiation in SCCs ($p = 0.8251$) did affect the local recurrence rate, respectively. In LM patients with recurrence, 3 out of 4 patients had punctate hyperpigmentation in the treated field 4 weeks after the end of RT. As postinflammatory hyperpigmentation cannot be differentiated from a persistent lesion, a regular follow-up with a timely histological analysis should be done in these patients. Immunosuppressed patients are not only known to have an up to 90 times increased risk of developing skin cancer [41, 42], but also to follow a more aggressive course [43]. In our study, however, the status of immunosuppression did not differ significantly between the patients who developed and who did not develop a relapse (11.4 vs. 14.2%, respectively, $p > 0.05$).

Treatment tolerability in RT with grenz and soft X-rays is good as the therapy-induced acute radiodermatitis occurs only within the treated site and heals within 4–6 weeks after completion of treatment [27, 28, 36]. In our cohort, neither grade >3 adverse events nor major disfigurement occurred. One patient with a medial canthus lesion developed a canalicular obstruction during treatment, which is a known complication of intervention in this anatomical area [44, 45], and this was treated with a punctal dilation by the ophthalmologist. To preserve the integrity of the drainage system, Berman et al. [27] suggested to place a nasolacrimal stent prior to the start of RT in the medial canthus. We also recommend planning a dermatological follow-up appointment 4 weeks after the last irradiation session for an evaluation of early side effects and referral to a specialist, if needed, as well as for an assessment of treatment efficacy.

In conclusion, RT with grenz and soft X-rays is a reasonable therapy modality for periocular skin malignancies, especially in patients of advanced age or if patients present with significant comorbidities. It provides high efficacy with limited side effects and good cosmetic outcome. However, local recurrences can occur, and therefore a regular clinical follow-up for at least 24 months after successful irradiation therapy is crucial.

Key Message

Radiotherapy with grenz and soft X-rays is a valuable and safe treatment modality for periocular skin malignancies.

Statement of Ethics

Subjects have given their informed consent. The study protocol was approved by the Ethics Commission of Canton Zurich (KEK-ZH 2017-00986).

Disclosure Statement

The authors have no conflicts of interest to declare.

Author Contributions

D. Lazarevic and E. Ramelyte take responsibility for the integrity of the data and the accuracy of the data analysis. R. Dummer and L. Imhof contributed to the conception of the work and critically revised the manuscript for important intellectual content. L. Imhof supervised the study.

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