

RESEARCH ARTICLE

Radiation Therapy for Primary Eyelid Cancers in Tunisia

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Abstract

Management of eyelid cancers is based on surgery and/or radiotherapy (RT). The treatment objective is to control tumors with acceptable functional and esthetic outcomes. The aim of this study was to evaluate the results of radiation therapy in management of epithelial eyelid cancers, reviewing retrospectively the clinical records of patients treated in our institution from January 1989 to December 2013. We focused on clinical and histological features, treatment characteristics, tolerance and disease control. One hundred and eight patients (62 men and 46 women) were enrolled, with a mean age of 61 years [ranges 15–87]. The most frequent tumor location was the inner canthus (42.6%). Median tumor size was 21 mm [ranges 4–70]. Histological type was basal cell carcinoma in 88 cases (81.5%), squamous cell carcinoma in 16 (14.8%) and sebaceous carcinoma in 4 (3.7%). Radiation therapy was exclusive in 67 cases (62%) and post-operative for positive or close margins in the remaining cases. Kilovoltage external beam radiotherapy (KVRT) was used in 63 patients (58.3%) and low-dose-rate interstitial brachytherapy in 37 (34.3%). Eight (7.4%) were treated with cobalt or with a combination of KVRT-cobalt, KVRT-electron beams, KVRT-brachytherapy or cobalt-electron beams. The total delivered radiation doses were 70 Gy (2 Gy/fraction) in 62 patients (57.4%), 66 Gy (2 Gy/fraction) in 37 (34.3%) and 61.2 Gy (3.4Gy/fraction) in 9 (8.3%). After a median follow-up of 64 months, we noted 10 cases of local recurrences (9.2%): 7 after exclusive and 3 after post-operative RT. No local recurrence occurred in patients treated with brachytherapy. Actuarial 5-year local recurrence-free rate, disease-free survival and overall survival were respectively 90%, 90% and 97%. T-stage was found to be a significant factor for recurrence ($p=0.047$). All acute radiation-related reactions were scored grade I or II. Delayed effects were eye watering in 24 cases (22.2%), eye dryness in 19 (17.6%), unilateral cataract in 7 (6.4%) and ectropion in 4 (3.7%). Radiation therapy and especially brachytherapy is an efficient treatment of eyelid cancers, allowing eye conservation and functional preservation with good local control rates and acceptable toxicity.

Keywords: Eyelid cancer - radiation therapy - brachytherapy - outcome - recurrence - cosmetic

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Introduction

Eyelid cancers account for 5% to 10% of all cutaneous malignancies and are mainly observed in elderly patients (Yin et al., 2015). The most common locations of these cancers are the inner canthus and the lower eyelid. Basal cell carcinoma (BCC) is the most frequent histological type accounting for more than 85% of cases (Deprez et al., 2009). Management of eyelid cancers is based on surgery and/or radiotherapy (RT). Complete surgical resection may be mutilating while RT offers the advantages of eye and function preservation. Adjuvant radiotherapy is indicated in patients at high risk of locoregional recurrence. Chemotherapy may be needed in some aggressive histological subtypes or in cases of nodal or metastatic dissemination.

Materials and Methods

We reviewed retrospectively the clinical records of

all cases of eyelid cancers treated in our department from January 1989 to December 2013. Only patients with lesions arising from eyelid skin were included. Patients with less than 12 months follow up were excluded from this study. Patient data were analyzed with regard to age at diagnosis, gender, tumor size and location, staging according to the seventh edition of the American Joint Committee on Cancer (AJCC) system for eyelid carcinoma (Ainbinder et al., 2009), histopathological features and treatment characteristics with focus on radiotherapy technique. Post-therapeutic outcomes focused on tolerance, patterns of recurrence, subsequent treatment, and survival.

Acute and late toxicities were scored by the Radiation Therapy Oncology Group (RTOG) scale (Cox et al., 1995) based on the notes reported in the clinical records.

Overall survival (OS), disease-free survival (DFS) and local control (LC) rates were calculated actuarially according to the Kaplan-Meier method. Chi-square Test and nonparametric tests were used for statistical analyses. A p -value <0.05 determined statistical significance for

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all tests.

Results

One hundred and eight patients, with histologically confirmed eyelid cancers, were included in this study. Mean age was 61 years [ranges 15-87]. Sixty-two patients were male and 46 were female.

The most frequent tumor location was the lower eyelid in 46 cases (42.6%). Other locations were internal canthus, higher eyelids, external canthus and both eyelids in respectively 26.8%, 17.6%, 6.5% and 6.5% of cases.

Tumor size at presentation ranged from 4 mm to 70 mm with a median of 21 mm.

Tumors were recurrent after a previous surgery without adjuvant treatment in 17 patients (15.7%).

Basal cell carcinoma (BCC) was the most common histological type, occurring in 88 cases (81.5%), followed by squamous cell carcinomas (SCC) in 16 cases (14.8%) and sebaceous carcinoma (SeC) in 4 cases (3.7%).

According to the AJCC staging system (3), 73 tumors (67.6%) were staged T1 or T2 and 35 tumors (32.4%) were staged T3 or T4.

Patients and tumor characteristics are summarized in Table1.

Radiation therapy was exclusive in 57 cases (52.7%) and post-operative for positive or close surgical margins in the remaining cases.

Kilovoltage external beam radiotherapy (KVRT) was used in 63 patients (58.3%) and low-dose-rate interstitial brachytherapy (LDRB) using 192 iridium wires (Figure 1) in 37 patients (34.3%). Eight patients (7.4%) were treated with cobalt or with an association of KVRT-cobalt, KVRT-electron beams, KVRT-LDRB or cobalt-electron beams. The total delivered radiation doses were 70 Gy (2 Gy/fraction) in 62 patients (57.4%), 66 Gy (2 Gy/fraction) in 37 patients (34.3%) and 61.2 Gy (3.4Gy/fraction) in 9 patients (8.3%).

Complete clinical response assessed 3-6 months after treatment (Figure 2) was obtained in 105 patients (97.2%). Three patients developed progressive disease and had subsequent orbital exenteration. The median follow-up for all patients was 64 months [ranges 12–336]. At the time of analysis, 3 patients died without evidence of recurrence. A local recurrence was observed in 10 patients (9.2%): 7

BCC, 2 SCC, and 1 sebaceous carcinoma. All these local recurrences were referred to surgery. There wasn't any local recurrence in patients treated with brachytherapy. None of the patients developed relapse in regional lymph nodes or at distant sites.

The 5-year actuarial LC, DFS and OS rates for all patients were 90%, 90% and 97% respectively (Figure 3). In the T1-T2 tumors group, we observed 2 local recurrences representing 2.7% of treated cases. In the T3-T4 tumors group, there were 8 recurrences accounting for



Figure 1. Brachytherapy Implantation for a Basal Cell Carcinoma of the Right Lower Eyelid



Figure 2. Complete Response and Good Esthetic Result after Brachytherapy

Table 1. Patient Characteristics

Characteristics	Patients number (%)
Age (years)	
< 60	44 (40.7%)
> 60	64 (59.3%)
Sex	
male	62 (57.4%)
female	46 (42.6%)
Histological type	
basal cell carcinoma	88 (81.5%)
squamous cell carcinoma	16 (14.8%)
sebaceous carcinoma	4 (3.7%)
Stage	
T1-T2	73 (67.6%)
T3-T4	35 (32.4%)

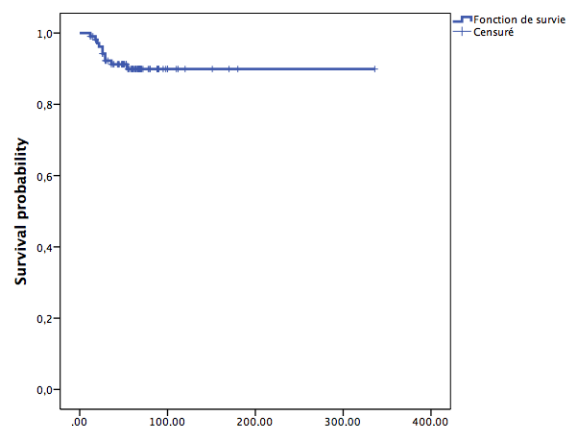


Figure 3. Recurrence-free Survival for All Patients

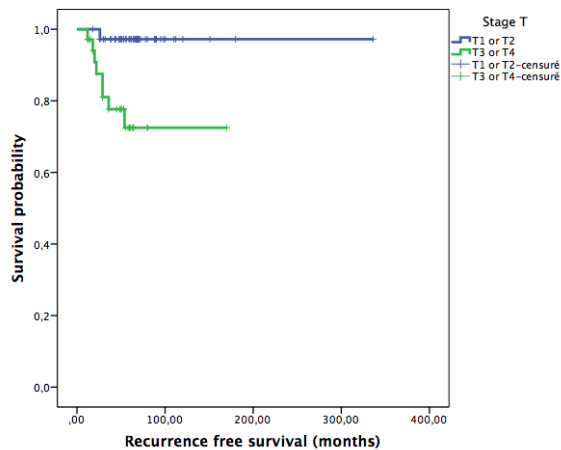


Figure 4. Recurrence Free Survival for Stage T1-T2 (Blue Line) and Stage T3-T4 Tumors (Green Line)

22.8% of cases. T-stage was found to be associated with higher recurrence rates ($p=0.047$) (Figure 4).

Acute radiation-related dermatitis, conjunctivitis or keratitis were noticed in respectively 100%, 79.6% and 22.2% of cases. All these reactions were scored grade I or II. Delayed effects were eye watering 24 cases (22.2%), eye dryness in 19 cases (17.6%), unilateral cataract in 7 cases (6.4%) and ectropion in 4 cases (3.7%).

Discussion

Our study showed that RT is an efficient treatment, allowing good control rates for eyelid carcinomas, especially for early stage tumors and when brachytherapy is used.

Management of eyelid malignancies requires different considerations from other cutaneous malignancies due to their location in the periocular region and the functional impact of complete surgical resection on ocular protection and visual function. Many factors may influence the therapeutic decision such as the age of the patient, its general status, comorbidities, tumor location and stage, histological type and prior treatments.

As in our study, basal cell carcinoma (BCC) is by far the most common histological type of eyelids cancers (Yin et al., 2015). The most common locations of eyelids BCC are the lower eyelid and the inner canthus (Jardel et al., 2015). BCC has the particularity to invade only adjacent structures with usually no risk of nodal or distant dissemination. The sclerodermiform subtype and medial canthus locations are associated with a higher risk of incomplete resection and a higher likelihood of local recurrence (Ho et al., 2012; Iuliano, 2012; Knani, 2014). Primary RT to the dose of 64-70 Gy (2 Gy/fraction) is indicated in inoperable cases or when complete surgical resection with adequate margins may cause functional or cosmetic damage. In our study, a total dose of 70 Gy was delivered in 57.4% of patients without major toxicities.

When surgery is indicated, minimal recommended surgical margins are 3-4 mm. More important margins of 5-10 mm are needed in recurrent BCC (other than superficial), in nodular subtype if the tumor size exceeds

1cm and in sclerodermiform, infiltrative and metatypic subtypes (Jardel et al., 2015). Such margins may be difficult to obtain safely in eyelids. Post-operative RT to the dose of 60 Gy in 30 fractions is proposed in case of positive or close surgical margins or extensive perineural involvement (Jackson et al., 2009).

Squamous cell carcinoma (SCC) accounts for 3.4 to 12.6% of eyelid cancers (Yin et al., 2015) and was the second histological type after BCC in our study. A part from habitual risk factors for skin cancers such as advanced age, sun exposure, fair skin and immunosuppression, infection with human papilloma virus was found to be associated with SCC of eyelids (Neale et al., 2013). Unlike BCC, SCC has a 24% risk to disseminate in regional lymph nodes. Parotid, preauricular and submandibular nodes are the most common sites of regional lymphatic dissemination. Distant metastases are present in nearly 6% of cases (Yin et al., 2015). Minimal recommended surgical margins are 4-6 mm except in high risk cases where wider margins (10 mm) are needed. Clinical high risk factors for locoregional recurrence are: tumor size > 1cm, poorly defined borders, immunosuppression, a tumor developed on a site of prior RT or chronic inflammatory process, a rapidly growing tumor, neurologic symptoms and recurrent tumors. Pathological high risk features are poorly differentiated tumors, adenoid, adenosquamous, desmoplastic or basosquamous subtypes, tumor thickness >2mm or Clark level IV-V and perineural, lymphatic or vascular involvement. Since wide margins are difficult to obtain in eyelids, post-operative RT is indicated in case of close or positive margins. Histological specimens should be carefully examined for evidence of perineural invasion, that is found in 8% to 14% of cases (Jackson et al., 2009). In case of perineural involvement, adjuvant RT is proposed to the dose of 60-70 Gy, depending on the surgical margins' status. Adjuvant RT is also indicated in case of lymph node involvement. Primary RT to the dose of 64-70 Gy (2 Gy/fraction) is indicated in inoperable cases and when complete surgical resection is at risk of cosmetic or functional impairment.

Sebaceous carcinoma (SeC) is a rare tumor of eyelids and was the third tumor in our study after BCC and SCC. If a patient presents with a history of multiple sebaceous carcinomas, a Muir-Torre syndrome which is a subtype of hereditary nonpolyposis colorectal cancer, should be suspected. A lack of expression of MSH1 or MSH2 was observed in SeC specimens from these patients (Gaskin et al., 2011). The most common malignancies associated with Muir-Torre syndrome are colorectal cancer, genitourinary cancer, and breast cancer.

SeC invades more frequently the upper eyelid and palpebral conjunctiva (Muqit et al., 2013). In a series of 60 patients with eyelid SeC, the local recurrence rate after surgical resection was 18% to 19.4% (Shields et al. 2004). Regional lymph node involvement is present in 8%-32% of cases, mainly in patients with AJCC stage T2b or more (Esmaeli et al., 2012). In a series of 13 locally advanced eyelid SeC (T3), patients who received adjuvant RT had a locoregional recurrence rate of 28.6% while 83.3% of patients who did not receive adjuvant RT developed locoregional recurrence (Deo et al., 2012). Despite

the low number of patients in this study, these results suggest the importance of postoperative RT in reducing locoregional recurrences in locally advanced eyelids sebaceous carcinomas. Adjuvant RT is also indicated in cases of positive or close surgical margins (< 5mm), nodal metastasis or perineural invasion (Connor et al., 2011, Hata et al., 2012).

Merkel cell carcinoma (MCC) is a rare and aggressive histological subtype of eyelid cancers, with 5% to 10% of MCC occurring in eyelids. Lymph node involvement is present in 20% to 60% of cases (Herbert et al., 2014). Wide surgical margins of 2-3 cm are necessary but are rarely achievable in eyelids. Adjuvant RT is recommended when the tumor size exceeds 1 cm, in case of lymphovascular invasion, immunodepression, close or positive margins, and recurrent tumors. In case of lymph node involvement, adjuvant RT and chemotherapy are indicated. Other histological subtypes such as melanoma, lymphoma and sudoral gland tumors are very rare in eyelids.

Sentinel node biopsy is recommended in eyelid melanoma when the tumor size is ≥ 1 mm, sebaceous carcinoma when the tumor size is ≥ 10 mm and in Merkel cell carcinoma (Pfeiffer et al., 2013).

Radiotherapy techniques used in eyelid cancers are adapted to the tumor volume. As in our study, low-dose-rate interstitial brachytherapy has excellent results in the management of early stage eyelid cancers with low long-term toxicity (Krengli et al., 2014). Nevertheless, in a large series of 850 eyelid cancers treated with external beam RT, local control rates were comparable to brachytherapy (Schlienger et al., 1996). More recently, high-dose-rate brachytherapy was used in eyelid cancers with encouraging results (Mareco et al., 2015). Kilovoltage external beam RT and electron beams are also widely used in superficial eyelid cancers. The ease of shielding and the ability to minimize field size argue in favor of kilovoltage x-rays for early-stage eyelid cancers (Amdur et al., 1992). Photons are more penetrative and may be used in advanced stages with deep structure invasion.

In conclusion, exclusive or adjuvant radiation therapy allows good local control rates in eyelid cancers with ocular conservation, functional preservation and low toxicity when adapted techniques are used. A broad collaboration between ophthalmologists, pathologists and radiation oncologists, in a multidisciplinary approach, is mandatory to insure the best treatment for patients.

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