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Review

Interventional Radiotherapy (Brachytherapy) in Eyelid and Ocular Surface Tumors: A Review for Treatment of Naïve and Recurrent Malignancies

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Key Words
Eyelid • Ocular tumor • Brachytherapy • Interventional radiotherapy • Conjunctival tumor

Abstract
The goal of radiotherapy in the treatment of eyelid and ocular surface tumors is to eradicate tumor burden in a manner that maintains visual function and preserve surrounding sensitive ocular tissue. Interventional radiotherapy (IRT-brachytherapy) is a radiotherapy technique associated with a highly focal dose distribution, with the advantage of boosting limited size target volumes to very high dose while sparing normal tissue. The reduction in the ocular and adnexal complications that result from this form of therapy, has led in recent years, to an increase in the use of IRT for the treatment of eyelid and ocular surface tumors. For eyelid malignancies, IRT is used as an independent treatment in small eyelids tumors, in postoperative treatment of high-risk patients and as well as salvage therapy in local recurrences. In the treatment of conjunctival malignancies, due to the high risk of local recurrence, the use of adjuvant therapies as IRT has shown to improve outcomes. In this review, we focus on eyelid and ocular surface IRT techniques and provide an overview of indication, outcomes and toxicity of IRT for the treatment of naïve and recurrent eyelid and conjunctival tumors.

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Introduction

Radiotherapy (RT) is one of several treatment modalities apart from surgery, laser, cryotherapy, and chemotherapy which can be used for ocular tumors [1].

Beside local tumor control and preservation of the eye, vision-preserving surgery is the current preferred primary treatment with this aim. However, extensive resection inevitably causes vision damage and disfigurement causing lid function changes. Furthermore, in order to keep sufficient surgical margins are often difficult to achieve and limited resection has a high risk of local recurrence.

Eyelid and ocular surface tumors are a therapeutic challenge, as the involved tumor tissues need a high therapeutic radiation dose, while surrounding health morphology like cornea, lens, retina and optic nerve are sensitive for radiation but also important for vision and therefore should be spared.

RT may be delivered as alternative to surgery, and is called exclusive, or may be delivered in combination with surgery. When combined with surgery timing of RT may vary significantly therefore it is defined neo-adjuvant when it precedes a surgical procedure, adjuvant when it is performed after surgery, intraoperative when it is delivered during the surgical procedure or perioperative when dedicated devices are placed during the surgical approach but the radiation treatment is delivered subsequently. Both external beam radiotherapy (ERT) and interventional radiotherapy (IRT- brachytherapy) are used in clinical practice [2]. With RT, it is often difficult to reach high doses to the target volume while sparing adjacent normal tissues, consequently resulting in undesirable side effects. Most common eyelids late effects include eyelid deformity, dry eye syndrome, discoloration, skin thinning and telangiectasia [3]. Functionally, these changes affect both the ability of the eyelid to adequately cover the epibulbar surface as well as retaining a smooth and stable protective film leading to a profound compromise in eyelid function with consequent devastating effects on the ocular surface. Direct side effects of ERT on the conjunctiva can lead to the development of extensive symblepharon formation, while on the cornea epithelial defects and ulceration can develop. Secondary vascularization, opacification, and perforation of the cornea can result as serious complication from above pathologies [4].

IRT has the great advantage to deliver a high target dose limited directly to the primary tumor volume, thus maximizing tumor dose while minimizing dose to nearby normal organs due to a rapid fall-off [5]. For example, it is possible to treat the orbit, in cases of uveal melanoma with extra-scleral extension, without damaging the visual function or causing side-effects to the sclera [6].

IRT involves the temporary placement of radioactive sources directly into a tumor (interstitial) or at superficial tumors, directly adjacent to the tumor laid over the lesion (contact). It can be delivered by several different means according to the type of implant using needles, dedicated applicators or plaques that can be customized to the individual tumor characteristics [7]. A renewed interest towards IRT has been demonstrated by several surveys performed at national levels [8-10].

Aim of this narrative review is to give an overview of the indications, treatment modality and side effects when IRT is used for eyelid and ocular surface tumors. In order to pursue such aim, we performed an extensive literature search of the available english literature without applying any time restriction. We included the largest and most uptodate series in this narrative review.

Results: Eyelid

Eyelid tumors are relatively uncommon, representing <3-5% of all skin cancers in the head and neck region with an incidence of 15 cases per 100,000 individuals per year [11].

Basal cell carcinoma (BCC) is by far the most common of eyelid non melanoma cutaneous malignancy, accounting for 86% to 96% of all cases; other non-melanoma cutaneous lesions

of the eyelid malignancies that occur in the periocular area include, in decreasing order of frequency, squamous cell carcinoma (SCC), sebaceous carcinoma (SebCa), and Merkel cell carcinoma (MCC).

BCC can recur locally with a rate of 1% at 5 years with negative margins, and up to 38% at 5 years with incomplete excision. The rate of metastasis of BCC is extremely low (0,03%).

SCC is more aggressive and invasive, local recurrence rate range from 2.4-to 36.9% at 5 years, the incidence for regional lymph node metastasis has been reported to be as high as 24%, while distant metastasis are reported in 6.2% of cases. SebCa is an aggressive malignancy with a great potential to spread to regional lymph nodes, local recurrence are seen in 6-29%of cases, 14-25% of patients develop metastases, either in the form of lymphathic spread to the lymph nodes and /or hematogenous spread to the liver, lungs, brain and bones. The most common periocular sites of BCC and SCC involvement are the lower eyelid and medial canthus; SebCa arise two or three times more frequently in the upper eyelid than its lower counterpart due to the presence of more meibomian gland in the upper eyelid compared to the lower [12, 13].

Malignant melanoma of the eyelid comprises 6% of malignant lesions of the eyelid and it is associated with a poor prognosis [14]. The standard of care for eyelid carcinoma is surgical excision with frozen section control of margins, the recommended safe margin of excision varies by histologic subtype, 2-3 mm clear clinical margin may be appropriate for BCC, whereas larger margin may be needed for more aggressive carcinomas, such as SCC, SebCA and MCC. Moh's micrographic surgery has been advocated for eyelid malignancies to ensure maximal preservation of normal tissue and to obtain margins free of disease [15].

However, because of its location in the periocular region, eyelid carcinoma surgery may produce severe dysfunction due to the functional impact of surgical resection and reconstruction on ocular protection and visual function; besides it can be associated with poor cosmesis [16]. RT mostly as ERT has been historically added in cases having high chances of local recurrence, positive or close margin, perineural invasion, primary treatment of advances disease or palliative treatment [17, 18].

The major hindrance in application of post-operative ERT is the close association of vital structures of the globe and the skin around the eyelid. Radiation-induced ocular morbidity encompasses a spectrum from transient eyelid erythema to complete loss of vision or loss of the globe [19, 20].

For the treatment of eyelid tumors, ERT can present technical concerns and complications due to the thin subcutaneous layer of the eyelid, the relevant curvature of the eye, and the dose to underlying structures [21].

IRT is considered as a therapeutic option which optimizes the balance between high radiation dose for the tumor treatment and sparing health tissue. The main reason for this is rapid dose fall-off for IRT [22]. IRT can be delivered by superficial (with dedicated commercial or customized applicators) or interstitial applications (with hypodermic needles or catheters) for eye lid tumors [23, 24]. In both cases, IRT allows to place applicators in contact or inside the target, which makes it possible to administer high doses within the clinical target volume (CTV) [25].

The rapid decrease in the dose with the growing distance from the applicator allows for the protection of adjacent structures; the lower percentage depth dose, is a better choice than ERT for treating small and accessible tumors. Moreover, IRT can be performed in unfavorable locations, such as the canthi [26-29].

In literature the use of IRT for eyelid tumors has been reported as independent treatment in small tumor size, in postoperative treatment of high-risk patients (positive or close margin, perineural invasion), as well as a salvage treatment in local recurrences.

The patient population treated by IRT and reported in the literature was heterogeneous in terms of histology (BCC, SCC, SebCA and MCC) and the total dose delivered (ranging from 26 to 63 Gy). The source used was Iridium-192 for non-melanocytic eyelid cancer and Iodine-125 for more aggressive melanoma eyelid cancers. A stainless-steel shield was

attached to the extraocular muscles to protect the ocular surface and deeper structures for the latter patients treated with Iodine 125 for melanoma eyelid cancer [14].

Both low-dose –rate (LDR) and high -dose-rate (HDR) IRT may be used [30].

When dealing with LDR-IRT, the treatment usually involves several days, thus requiring hospitalization, because the total dose is released continuously from the application of the radioactive sources until its removal requiring strict radioprotection rules for the staff. On the contrary modern radiotherapy using HDR-IRT with remote after-loader machines, allows to deliver the total dose without the need for hospitalization since no radioactive sources are placed within the patient. The total dose is usually fractionated to avoid potential toxicity to surrounding normal tissues [31].

Interstitial HDR-IRT is performed under local or general anesthesia and aseptic conditions. Rigid hollow stainless-steel needles are inserted into the treatment area, parallel and equidistant to each other in a single plan. The implant geometry has to follow the Paris-System geometry rules for monoplanar implants [32]. Plastic and flexible catheters are then inserted into these hollow needles and left in place with subsequent removal of metal needles. The plastic tube ends are then fixed to the skin with sutured plastic buttons.

CT scan should be used to verify the radiation target area, the position of the catheters and to make the dosimetry evaluation of the treatment plan.

While contact HDR-IRT usually does not require any anesthesia and may be performed by custom-made surface moulds or other types of applicators commercially available. Custom-made molds are usually manually built from impression of the tumor surface using conventional thermoplastic- or silicon based bicomponent materials. Standard plastic catheters are embedded and/or attached on the mask surface [33]. Also, in this case CT scan is obligatory to verify the correct position of the catheters within the target and to make the dosimetry evaluation of the treatment plan. Most common acute side effects following IRT are conjunctivitis and radiodermatitis, very rarely corneal ulcerations; the most common late effects are keratoconjunctivitis, madarosis, less frequently epiphora, lacrimal duct stenosis and scaring. Recurrent lesions and higher volumes receiving the prescribed dose are associated with worst cosmetic outcomes.

A summary of the main findings about radiotherapy in eyelid tumors is reported in Table 1.

In Fig. 1 is shown an eyelid implant; in Fig. 2 is shown a salvage treatment of BCC recurrence; in Fig. 3 is shown a primary SCC treated with interstitial implants.

Table 1. Summary of the main findings about radiotherapy in eyelid tumours

Author	Year	n. of patients	Tumor characteristic	Treatment Characteristic/ Isotope	DoseGy/Fraction	Toxicity	Median follow-up (months)	Local control
Cisek et al. [3]	2021	28	BCC (86%) SCC (14%)	Interstitial HDR / Ir192 source	45-49Gy/5-14	Eyelid deformity (35%) Dry eye syndrome (55%) Pigmentation changes (80%)	22	97%
Vavassori et al. [33]	2019	9	BCC (56%) SCC (22%) NHL (11%) Pla (11%)	Contact HDR / Ir192 source	30-48Gy/10-17	Pigmentation changes (44%) Corneal ulceration (11%)	51	100%
Laskar et al. [29]	2015	8	SbCC (50%) SCC (37.5%) BCC (12.5%)	Interstitial HDR / Ir192 source	21-35/7-10	Pigmentation changes (14%) Ectropion (14%)	34.5	100%
Mareco et al. [31]	2015	17	BCC (94%) SCC (6%)	Interstitial HDR / Ir192 source	42.75/10	Madarosis (65%) Keratoconjunctivitis sicca (46%) Eyelid malocclusion (46%) Pigmentation changes (47%)	40	94.1%
Azad et al. [28]	2011	20	SCC (50%) SbCC (40%) BCC (10%)	Interstitial HDR / Ir192 source	39/6	Madarosis (70%) Lid fibrosis (15%) Depigmentation (10%) Keratitis (5%)	39.5	75.6% (5years)
Conil et al. [26]	2004	23	BCC (79.2%) SCC (26.7%) Adenocarcinoma (4.2%)	Interstitial LDR / Ir192 source	40/1	Madarosis(100%)	43	91.6%
Stannard et al. [14]	2000	14	Eyelid and palpebral conjunctiva melanoma	Iodine seeds in polythene tubes	17.3-67.6Gy	Loss of eyelashes Mild eyelid atrophy and teleangectasia Cataract (7%)	45	93%

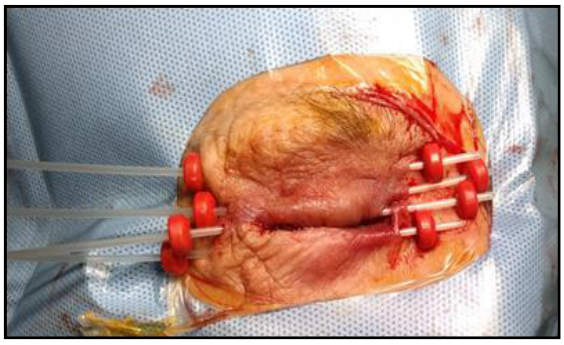

Fig. 1. Eyelid implant in the operating room.

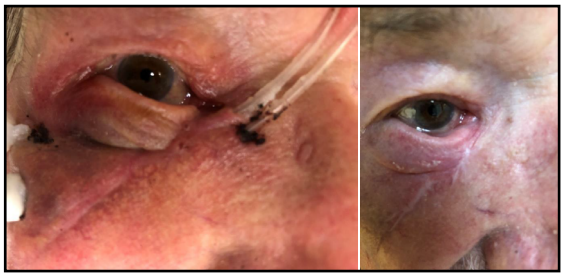

Fig. 2. A salvage treatment of a 2nd BCC recurrence after surgery and actually not completely resected.

Fig. 3. Primary SCC treated with interstitial implants with plastic tubes and irradiated following CT based personalized dose planning.

Results: Ocular surface tumors

IRT is the ideal modality for managing ocular surface malignancy as the radiation is adsorbed at an exponential rate inversely proportional to the distance from the isotope. Thus, the highest concentration of the radiation is delivered to the tissue most requiring treatment, the conjunctiva and the corneoscleral bed, minimizing irradiation of deeper structures [34].

In the treatment of ocular surface tumors, IRT involves the use of a device filled with radioactive isotopes (Ruthenium-106, Iodine-125, Sr-90) placed to the ocular surface after surgical excision w/o cryotherapy to secure the surgical margins.

When using Sr-90, the radioactive dose is delivered by a handheld device, while both Ru-106 and I-125 are sutured to the ocular surface, allowing a more precise plaque localization [35].

Ocular surface tumors encompass a broad spectrum of neoplasms, the most common malignancies include ocular surface neoplasia (OSSN) and melanoma [36]. Ocular surface squamous neoplasia (OSSN) represent a spectrum of disease ranging from mild dysplasia

to invasive SCC. Conjunctival SCC generally involves the limbal region; usually remains on the surface of the globe but intraocular invasion is found in 3-9% of cases [37]. The overall prognosis of SCC is good, and the mortality rate is low, but there are reports of regional invasion, distant metastasis and intracranial invasion [38]. Conjunctival SCC management depends on tumor location and size and usually involves surgical excision with wide margin, alcohol –treated limited superficial keratectomy, and adjuvant cryotherapy [39]. Recurrence following wide excisional biopsy combined with cryotherapy are low at 8% to 16% [40].

Topical medications can be useful for primary or secondary treatment of conjunctival SCC using mitomycin C (MMC), 5-fluorouracil, and interferon alfa-2b. Plaque IRT can be used to control residual microscopic tumor following surgical resection of conjunctival SCC or in cases of deep scleral or corneal invasion [5]. Initial reports on beta radiation using strontium-90 revealed nearly 100% success rates in cases of superficial conjunctival SCC. Similar results have been observed with Ruthenium-106. For invasive conjunctival SCC, those with defined deep /scleral or corneal stromal) invasion, gamma radiotherapy using Iodine 125 has also been explored as an adjunctive treatment to excision [23]. The literature describes 116 cases of conjunctival SCC treated with surgical excision followed by adjuvant IRT. Of those 116 conjunctival SCC cases, 7 recurred during variable follow-up periods, resulting in an average recurrence rate of conjunctival SCC managed by excision adjuvated by IRT of 6.0% [41].

Conjunctival melanoma is the second most frequent malignant neoplasm of the conjunctiva after squamous cell carcinoma. Conjunctival malignant melanoma (CMM) is a rare but potentially life-threatening cancerous growth of the eye [42]. Survival is largely dependent on the location of the tumor, those on the bulbar conjunctiva (Stage T1) having a much better prognosis than those of the palpebral conjunctiva, fornixes, plica, caruncle, or eyelid margin, where the mortality is 2.2 times higher [43]. Despite close surveillance and intensive therapy at subspeciality centers, CM shows a five-year local recurrence rate from 26% to 61% and one of the most important risk factors for local recurrence include non-bulbar tumor location.

The standard treatment for these tumors is excision together with adjunctive therapy consisting of cryotherapy, chemotherapy or IRT. IRT can be performed using Strontium-90, Ruthenium-106 (Ru-106), or Iodine-125 (I-125), after excision and it is usually delayed until the conjunctiva has healed. RT, as adjuvant therapy after excision, has been reported to reduce the rate of local recurrence in comparison to excision alone, excision with cryotherapy, or excision with mitomycin C [44]. In T1-classified CMM, those with an epibulbar location, IRT using plaque is the most favored treatment [45].

Plaque IRT for epibulbar tumors can be performed with I125 and Ru 106 isotopes or with Sr90. In literature a treatment dose of 100 Gy prescribed at a depth of 1-3 mm has been reported for Ruthenium plaque and Iodine seeds and 60 Gy prescribed at the conjunctival surface for Stronium 90 applicator; the dose is delivered after the conjunctiva has healed from excisional biopsy [46, 47].

In the treatment of surface ocular tumors using IRT, radiation complications reflect the anterior plaque location. The most common ocular complications described are cataract, transient corneal epithelial defect, rarely scleral necrosis. Long-term irritation and dryness post radiation treatment to the eye are often described [48].

A summary of the main findings about radiotherapy in ocular surface tumors is reported in Table 2.

In Fig. 4 is shown the case of a conjunctival melanoma located at temporal limbus with early corneal invasion treated with excision, amniotic membrane apposition and adjuvant Ruthenium plaque.

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Table 2. Summary of the main findings about radiotherapy in ocular surface tumours

Author	Year	n. of patients	Tumor characteristic	Treatment Characteristic/ Isotope	Plaque treatment and depth(mm)	DoseGy/Fraction	Toxicity	Median follow-up (months)	Local control
Brouwer et al. [47]	2021	58	Conjunctival melanoma	Plaque brachytherapy	Strontium90 (conjunctival surface) Ruthenium 106 (2mm)	60Gy (Sr) 100Gy (Ru)	Pain (29%) Dry eyes (21%) Symblepharon (9%) Ptosis (12%) Cataract (9%)	143 (Sr) 40.2 (Ru)	79% (5 years)
Fagerberg et al. [41]	2021	2	Conjunctival SCC	Plaque brachytherapy	Ruthenium 106/ 2mm	100Gy	None	32	100%
Laskar et al. [29]	2015	13	SCC Meibomian gland carcinoma Bowenoid actine keratosis NHL MALT	Strontium 90 applicator 12mm diameter	Strontium 90	30-50 Gy (single-dose treatment)	Limbal scar (7.7%) Opacification at limbus (7.7%)	51	90.9%
Arepalli et al. [37]	2014	15	Conjunctival SCC	Plaque brachytherapy	Iodine 125	50-80Gy	Cataract (87%) Iris teleangectasia (34%) Corneal epithelial defect (27%) Corneal edema (20%) Glaucoma (6.7%)	42	100%
Karim et al. [48]	2010	19	Conjunctival melanoma	Plaque brachytherapy	Iodine 125/1.5-3mm	100Gy	Corneal ulceration (31%)	43	100%
Damato et al. [46]	2009	40	Conjunctival melanoma	Plaque brachytherapy	Ruthenium 106/1-2mm	100Gy		19.2 32.4	
Walsh-Conway et al. [34]	2009	11	SCC (54.5%) CM (45.4%)	Plaque brachytherapy	Iodine 125/1.5-2.5mm	100Gy	Corneal ulceration(45%)	23.4	100%

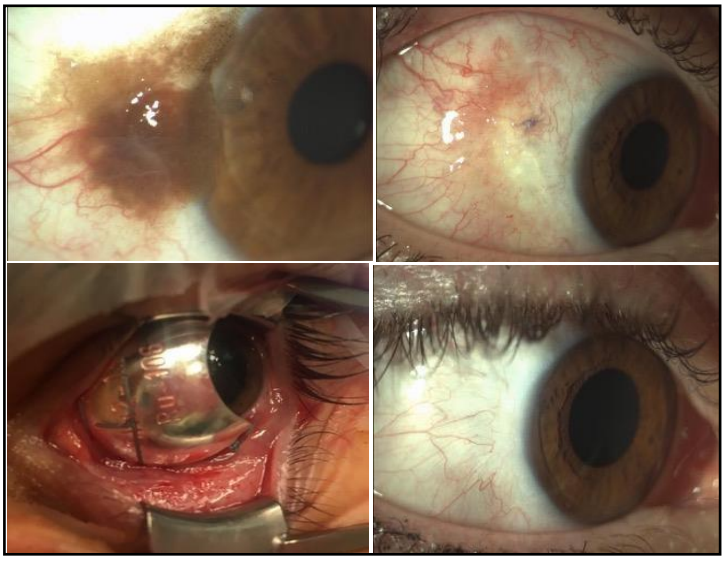

Fig. 4. A: Conjunctival melanoma located at temporal limbus with early corneal invasion. B: Appearance 1 month after excision and amniotic membrane apposition. C: Ruthenium plaque adjuvant treatment. D: Appearance of the area shown in Fig. A, two years after surgery, amniotic membrane apposition and Ruthenium plaque, showing no recurrence.

Results: Pterygium

Tumors of the nonbulbar conjunctiva (fornix, caruncle, eyelid) or with orbital extension are not accessible to plaque IRT as adjuvant treatment after excision. In these cases, ERT or proton beam radiotherapy (PRT) are used as possible adjuvant therapeutic options [49]. Alternatively, an I-125 or an Iridium-192 IRT interstitial implant can be used with shielding of the cornea and lens. A special situation is represented by a benign tissue proliferation, the pterygium. It affects visual acuity when it spreads to the cornea, especially when near the level of the pupil margin and irradiation could be considered alternatively to Mitomycin-C and autografting methods [50, 51].

Discussion

Interventional radiotherapy is an effective and well tolerated modality for the management of patients with eyelid and ocular surface malignancies.

For eyelid tumors interventional radiotherapy (IRT-brachytherapy) can be used either as primary or as adjuvant therapy. In the treatment of ocular surface tumors interventional radiotherapy is mainly reserved as adjuvant treatment following surgery for incompletely

resected SCC, who display multiple recurrences or in case of a deep infiltration of sclera or cornea. In the treatment of conjunctival melanoma, due to the high risk of recurrence, adjuvant treatment with interventional radiotherapy is strongly recommended. For tumors with epibulbar location, interventional radiotherapy can be delivered using a plaques sutured to the sclera; in case of non-bulbar conjunctiva involvement a reverse plaque or an interstitial approach can be considered.

IRT of the orbita/periorbital region should exclusively be performed in a multi-disciplinary setting by experienced radiation oncologists and ocular oncologists.

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Author Contributions

Monica Maria Pagliara: Manucript conceptualization and writing. Vinodh Kakkassery: Manucript conceptualization and writing. Bruno Fionda: Literature search. Domenico Lepore: Literature search. György Kovács: Critical revision and final approval. Luca Tagliaferri: Critical revision and final approval. Maria Antonietta Blasi: Critical revision and final approval.

Disclosure Statement

The authors declare that no conflicts of interest exist.

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