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*Review*

# Radiotherapy of Conjunctival Melanoma: Role and Challenges of Brachytherapy, Photon-Beam and Protontherapy

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**Abstract:** Conjunctival melanoma is a rare neoplasia, whose therapeutic management is generally of ophthalmological relevance, through radical surgical resection. The high incidence of local relapses after surgery, has made it necessary to combine various types of adjuvant treatments, which in some cases take on the role of radical treatments. Among these non-surgical treatments, those involving the application of ionizing radiation are becoming particularly important. In this review, we discuss the role of episcleral brachytherapy, external photon-beam radiotherapy, also made through stereotactic or radiosurgical modality, and of proton-beam radiotherapy. We try also to take stock of the benefits of the different irradiation modalities and the application difficulties of each.

**Keywords:** Conjunctival melanoma; episcleral brachytherapy; proton-beam radiotherapy

## 1. Introduction and General Overview

Conjunctival melanoma (CM) is a rare ocular disease, accounting for about 2% of all ocular malignancies. Its incidence has been increasing in recent years, with 0.3–0.8 cases per million people in Western countries, mainly in Caucasian ethnicity, but can occur in African or in Afro-Americans as well. It most commonly appears in middle-aged or elderly white individuals. In the US, the incidence increased by 295% from 1973 to 1999 [1–3].

Usually, it arises from primary acquired melanosis (PAM), in about 75% of cases, less frequently from a pre-existing conjunctival nevus or de novo. CM arising from PAM appears as a thickening lesion. Histopathologically, PAM with mild atypia has less likelihood of transformation to melanoma than PAM with severe atypia [4].

De novo melanomas carry a higher risk of metastasis and death. As in cutaneous melanoma, sun exposure is a high risk factor and plays an important role in the pathogenesis of CM.

Clinically, CM appears as a nodular or flat pigmented lesion, commonly located on the nasal or temporal bulbar conjunctiva (Figure 1), and, less frequently, as amelanotic tumors. It has a tendency to spread directly to any part of conjunctiva, to the cornea, globe, eyelid, orbit, sinus or central nervous system, and through lympho-vascular drainage to the laterocervical lymph nodes or distant organs, as reported in the AJCC eighth edition staging system [5,6]. Pathologic staging is based on vertical thickness and depth of invasion, and, consequently, it is classified as follows: ≤0.5, 0.5–1.5, and >1.5 mm. Breslow stages are not routinely used to classify CM.

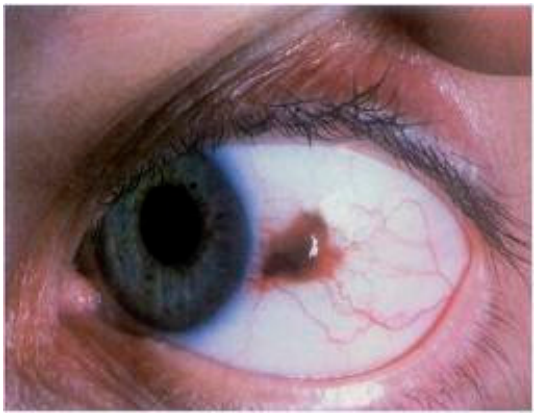

**Figure 1.** Slitlamp photograph of a conjuntival melanoma, histologically confirmed, with a tendency to invade the limbus and cornea.

Biologically, CM shows different behavior than uveal melanoma, while it is quite similar to that of its cutaneous counterpart. Molecular characterization studies, developed to understand the tumor biology and possibly to implement any new therapeutic approaches, have confirmed this similitude with cutaneous melanoma. In particular, Griewank et al. found BRAF (of which, 91% were V600E) mutations in 29% and NRAS in 18% of conjunctival melanoma analyzed, similar to cutaneous melanomas [7].

Diagnosis requires a complete examination of bulbar and tarsal conjunctiva, as well as orbital rim, due to the high rate of recurrence in that region. Opthalmic examination, slit-lamp photography with clinical drawing, in vivo confocal microscopy (IVCM), optical coherence tomography (OCT), and ultrasound biomicroscopy (UBM) are variably used for documenting the localization and size of the lesion and to study its local extension. These non-invasive imaging techniques could support the diagnosis, but the excisional biopsy of a clinically suspicious lesion is undoubtedly the standard of care.

CT and MRI of the orbit, maxillofacial region and brain are useful when an orbital, nasal and paranasal sinus or central nervous system involvement is suspected. Whole body PET/CT scan or MRI of the neck can reveal lymphatic spread to proximal nodes, and metastatic disease to regional lymph nodes is accessed using sentinel lymph node biopsy (SLNB) [8].

Surgery is the mainstay of treatment. Shields introduced in 1997 the "no touch" technique, describing surgical guidelines to allow a complete en-bloc tumor removal with wide margins, avoiding direct tumor manipulation [9]. This technique is widely accepted and applied, in order to minimise cell seeding and reduce the likelihood of recurrence. Incisional biopsy is discouraged, as well as narrow-margin resection; a margin of at least 2 mm is generally advised, though some surgeons

suggest 5 mm when possible. In case of suspect involvement of the Tenon capsule, or when there is any evidence of scleral adhesion or pigment, a local dissection to these structures should also be performed.

Less frequently, CM presents as extensive infiltrating tumor, requiring enucleation or orbital exenteration. This is the case of eyes with limbal lesion, tumors underwent multiple resections, painful eyes and unacceptable cosmesis.

Intraoperative adjuvant treatments are often performed to the exposed scleral base and surrounding conjunctival margins to destroy possible remaining tumor cells. These include a variable combination of different adjuvant treatments: absolute alcohol application, Mitomycin C (MMC) or Interferon-alpha-2B instillation, double freeze–thaw cryotherapy. Cryotherapy works by freezing the cells and then producing ischemia from the disruption of the microvasculature; it showed to be superior in preventing the tumor recurrence than surgical excision alone, with a recurrence rate of 18% vs. 52% [10]. Topical chemotherapy treats the entire ocular surface in eyes with poorly defined tumor margins, which allows for the treatment of diffuse or multifocal lesions, or occult areas. Recurrence rates after treatment with adjuvant MMC range from 33 to 50% [11].

Lymphatic spread to the neck lymphnodes can be detected with 18F-FDG-PET or, when microscopic, with SLNB.

Despite surgical and intraoperative adjuvant treatments, CM have a high incidence of local recurrence, about 50–60% at 5 years. The recurrence rate is lower with the use of combined radiotherapy treatment [12]. The use of adjuvant radiotherapy is widely increasing, mainly by means of brachytherapy. Application of external-beam conventional X-rays techniques, stereotactic and radiosurgery, or proton-beam radiotherapy is less frequent and long-term results are awaited. Here, we describe the different radiotherapy techniques, focusing on the benefits and application difficulties of each.

## 2. Brachytherapy

The standard treatment of primary conjunctival melanoma (CM) is local excision followed by adjuvant local therapy or only brachytherapy. This treatment modality is increasingly safe, effective and ever-expanding, although most of the experiences reported in the literature refer to its use for uveal melanoma in which it is considered a standard treatment for small or medium-sized tumors, ≤10 mm in apical height and ≤16 mm in diameter [13,14].

In CM, adjuvant treatment is important to improve tumor control and patient survival, especially when surgical margins are positive. Adjuvant therapy includes brachytherapy, cryotherapy, topical mitomycin C, proton beam radiotherapy, or alpha 2b interferon. Size and localization are important parameters of choice of these treatments to use [15].

Eye brachytherapy can use radionuclides emitting low-energy photons (125I, 103Pd, or 131Cs) or beta rays (106Ru/106Rh or 90Sr) [15,16]. Radionuclides emit several low-energy, in the X-ray range (20–35 keV), photons with different intensities. In this case, the photoelectric effect, in which photons transfer energy to electrons, is the predominant effect.

The choice of devices depends on the operator's experience, properties of the specific radio-isotope, size and the method of use [16,17]. Custom plaque design can reduce unnecessary radiation to nearby healthy structures, reduce treatment time and increase its effectiveness. The 131Cs source provides a slightly more uniform dose distribution than the other sources, but the DVHs of these plaques (I, Pd) show a similar trend. Palladium-103 has a biologically effective dose better than I-125. Due to the rarity of the disease, there is not numerous data on the various ways of delivering brachytherapy [17].

Currently, there is no standardized dose protocol for the irradiation of intraocular tumors with 106Ru eye plaques; in fact, there are two different methods of delivery (high dose: 290–320 Gy or low dose: 100 Gy), while, for I125 eye plaques, the minimum dose required for tumor control should be at least 85 Gy [15–19]. Iodine plaques are usually used to treat tarsal conjuntival melanoma after primary excision. Even for Sr-90 there is not a standardized regime, but, on average, the total dose is 36–60 Gy and fraction size is typically 10 Gy, and it is preferable for lesions of the bulbar conjunctiva for the shape and the size of the applicator. The technical characteristics of the applicators may constitute

a limitation for their use in cases where the ocular anatomy does not allow it. Strontium treatment using a hand-held applicator, and treatment is used in the Academic Medical Center (Amsterdam, the Netherlands) or Catharina Hospital (Eindhoven, the Netherlands) as in those centers a Sr-90 applicator was available. In these centers is dispensed a dose of 60 Gy in 6 fractions, 10 Gy at a time, at the conjunctival surface. The application lasts 60–90 s. While Ru-106 brachytherapy is used in Leiden University Medical Center (LUMC, Leiden, the Netherlands): 100 Gy in a single dose are dispensed in this center, 2 mm deep because all the lesions had been removed. Treatment time was variable and there were different types of plaques of different shapes and sizes. From 2012 onwards, in patients with primary acquired melanosis (PAM) in addition to CM, the topical use of mitomycin and brachytherapeutic treatment with Ru-106 [10,18].

There are no statistically significant differences in the development of relapses, metastases or deaths between the two treatments; according to Wong, even the treatment with I-125 plaque does not differ much from the results with Ru-106 and Sr-90, but Ru-106 reduces local toxicity compared to Sr-90 [15–18]. Moreover, the adjuvant treatment with Ru106 had the same total recurrence rate as the treatment performed by Damato, who applied the same dose at a depth of 1 mm [10]. Obviously, we compare different doses because the biological effect of radiation depends not only on the total dose, but also on the dose rate, on the fractionation and on the total treatment time. As Sr-90 is applied in short sessions, the dose rate is much higher compared with that of Ru-106 (103.2 Gy/h for Sr-90 versus 4.0 Gy/h for Ru-106). Another difference between Sr-90 and Ru-106 is that while Sr-90 is outpatient, Ru-106 needs hospitalization. The half-life of the Sr-90 is much longer than that of the Ru-106 (28.8 years versus 374 days) [9–18]. To date, Sr90 applicators are out of production, so it is pretty hard to find them; there is only one lobby that produces them.

However, studies between the various isotopes are unreliable due to the different size of the tumor, localization and surgical technical variable. Brachyterapy offers better results in terms of quality of life (eye preservation) and is comparable in tumor control over enucleation, but it is not without side effects, for example cataract (45%) (Maximum Doses-Dmax 25 Gy), telangiectasia (40%) (Dmax 104 Gy), episcleritis (5%) (Dmax 125 Gy), descemetocele (5%) and secondly pain, clouding of the lens, dry eye complaints or corneal erosions, symblepharon, ptosis, corneal ulcers and scleral necrosis [13–18]. No patient developed a new brachytherapy-induced tumor.

Radiotherapy Sr-90 appears to be safer and more effective than other adjuvant treatments (Mytomicin C) for melanoma conjunctival. So, the most frequent contraindication in radiotherapy is cataract, although vision can be restored with surgery. Another side effect of radiation therapy is permanent vision loss due to damage to the macula or optic disc; retinopathy is also an important risk factor for vision loss. In fact, the most radiosensitive structures of the eye are the lens, followed by the cornea, retina and optic nerve [19,20]. Local excision with adjuvant brachytherapy provides good tumour control with excellent visual outcome and mild side effects in patients with limited conjunctival melanoma. Results after Sr-90 or Ru-106 were comparable; a choice for either treatment may be based on experience of the clinician and availability of materials.

## 3. External Photon-Beam Radiotherapy

The rarity of conjunctival and iris melanoma and the wider use of brachytherapy and proton therapy have limited the use of external photon-beam radiotherapy.

In a recent meta-analysis on the role of radiotherapy in ocular melanomas [21], it is underlined that stereotactic radiation therapy (SRT) and stereotactic radiosurgery (SRS), mainly administered with gamma knife and cyber knife, represent an alternative therapy. Authors concluded that, for the small number of studies available on this topic and applied methodology, are not able to determine what the most effective radiotherapy technique is.

For small and medium-sized lesions, external photon-beam radiotherapy has shown similar efficacy and side effects to proton therapy [21]. Stereotactic radiosurgery with charged-particle beams

(carbon ions, protons) is effective in larger lesions with irregular margins, causing less adverse effect and less damages to surrounding organs at risk [22].

External beam radiation is also proposed as palliative treatments for nonresponsive, recalcitrant carcinomas for patients in whom conventional therapy has not been effective. After failure of multiple standard treatments, Graue et al. [23] treated a small patient's series with electron beam radiotherapy, but with curative doses (50 Gy in 2.5-Gy fractions or 60 Gy in 2.0-Gy fractions, approximately the same radiobiological equivalent dose). The local tumor control rate was 75%, with relatively few side effects; there were no second cancers.

There are selected cases in which photon beam radiotherapy can be proposed: when patients refuse or cannot have surgery, positive margins, negative surgical margins with presumed residual microscopic disease, such as adjuvant therapy [24], extra tumoral perineural infiltration, post-exenteration radiotherapy in high-risk patients, lymph node involvement and previous recurrence.

## 4. Proton-Beam Irradiation

Proton-beam radiotherapy (PBRT) is a good alternative to enucleation or exenteration in complex cases of conjunctival melanoma. These include cases with extensive eyelid, conjunctival or caruncular involvement, as an alternative to aggressive surgery [25,26].

PBRT has the advantage of precise dose release, better than other irradiation modalities. This ballistic advantage permit to release very high-dose gradients close to organs at risk (OAR), avoiding them and respecting their dose constraints [25].

So, it is feasible to treat accurate volumes with a homogenous dose on the target (unlike brachytherapy, which delivers highly inhomogeneous doses on target volumes) and to preserve structures in the direct neighbourhood of the target volume. To protect the tissues localized, only 1–2 mm behind the target volume, the dose can be reduced to zero, thanks to the distal dose fall-off of the Bragg Peak phenomenon. It is responsible for an increasing dose deposition of these particles as they travel through the tissue, with an approximately constant low entry dose, a region of high dose at a depth determined by the initial proton energy, and no dose beyond the end of the range [25]. The majority of Protontherapy centers use a 60–70 MeV proton beam to treat ocular tumors, as it happens at the Center Antoine-Lacassagne in Nice or at Catana Centre in Catania.

There are few reports on the use of PBRT for CM, unlike the great experience in the treatment of uveal melanoma.

Wuestemeyer et al. reported in a retrospective study the treatment of 20 patients with conjunctival melanoma. The dose was 31 GyRBE in 6 fractions with a boost of 14 GyRBE in two fractions on the main target (total dose 45 GyRBE). The median follow-up was 34 months. Local recurrence happened in six patients (30%). Three of them detect in the target volume which had received 31 Gy, two recurrences place outside the target volume and one was localized in the primary target volume (45 Gy). Patients with relapse underwent enucleation (2 pts), external radiation (1 pt), and 106-Ruthenium-plaque brachytherapy (2 pts). One patient refused further treatment. Six patients (30%) had distant metastases after 24.8 ± 13 months after PBI. A total of 19 patients developed a sicca-syndrome. A focal cataract developed in seven patients (35%). There was madarosis in the area of irradiated eyelids. In four cases, a limbal stem cell deficiency occurred with the consequence of corneal vascularization. None of the patients complained retinopathy, secondary glaucoma, iris neovascularization or optic disc neuropathy [26].

Scholz et al. reported in a retrospective study the treatment of 89 patients with conjunctiva melanoma from 1993 to 2015. The total delivered dose was 45 Gy with a 65 Mev proton-beam. The treatment was carried out in two phases: 31 Gy in six fractions on the main volume including the suspected areas of microscopic disease and a boost of 14 Gy in two fractions on the primary disease localization. The mean follow-up was 4.2 years. Twenty-nine patients (33%) experienced local recurrence: 16 inside and 13 outside the irradiation field. A total of 18 patients underwent exenteration: 16 with disease recurrence and two without. A total of 14 patients developed distant lymphatic or

hematogenous metastases. Fifteen patients underwent salvage therapy with chemo-immunotherapy (Mitomycin C/INF alpha), brachytherapy or external beam radiotherapy. Main collateral effects after proton radiotherapy were secondary glaucoma (11%) limbal stem cell deficiency (8%) and sicca-syndrome (30%) [27].

Thariat et al. reported in a retrospective study the treatment of 96 patients with conjunctiva melanoma from 1992 to 2018. The delivered dose was 45 Gy in eght fractions. In case of wide tumors with macroscopic and microscopic components, a two-step treatment was used with a large field including the full quadrants from limbus to conjunctival folds to 31.2 Gy and a reduced boost to the macroscopic lesion for 13.8 additional Gy. A brass collimator modeled the beam laterally to have 2.5 mm lateral margins around the involved conjunctiva. Mean follow-up was 4.7 years. Five-year local failure rate was 33.2%. Of 25 local recurrences, four were in-field, 14 were marginal/out-of-field, others were undetermined. Salvage exenteration was executed in 13 patients. During follow-up, glaucoma was reported in in 13 patients (14.1%) and cataract was reported in 22 patients (23.9%). Corneal thinning, conjunctival, and scleral perforation were reported in 11, 9 and 1 patients (22.9%), respectively. Madarosis, dry eye syndrome, conjunctival scarring, lachrymal duct stenosis were reported in 21 patients (22.8%), 28 (30.4%), 7 (7.6%), 5 (5.5%), respectively [28]. No second neoplasm has been found.

At Catana Centre in Italy, 14 patients have been treated in a period of 16 years. A personally shaped brass collimator was carried into the beam to adapt the range of the protons in a way that the conjunctival lesion was irradiated with an additional diameter of 2.5–3 mm (Figure 2). A single-step treatment was used, with four daily fractions of 15 GyRBE to a total dose of 60 GyRBE, borrowing the long-term experience gained with the treatment of uveal melanoma. After a median follow-up of 11 years, two local failures were reported, and a chronic conjunctivitis and dry eye syndrome were reported in four patients, without evidence of corneal or lacrimal ducts damage [29–33].

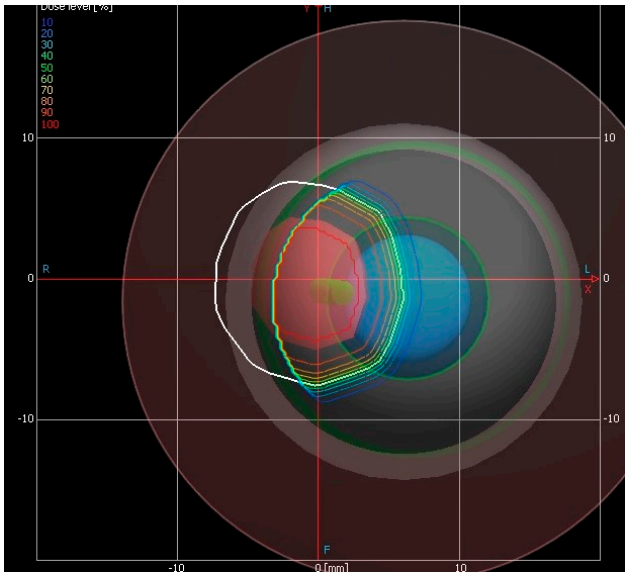


**Figure 2.** Beam-axis isodose view from the Eyeplan Treatment Planning System.

## 5. Conclusions

The radiotherapy methods that have been applied to the treatment of conjunctival melanoma are many and varied, and for each of them there are pros and cons. Historically, the use of radiotherapy in CM has mainly occurred in an adjuvant, perioperative modality, through the application of episcleral brachytherapy to the exposed scleral base and surrounding conjunctival margins to destroy possible remaining tumor cells. The use of EBRT (external-beam radiation therapy) techniques, especially in stereotactic or radiosurgical modality, is limited due to the risk of creating severe late damage to the

surrounding healthy tissues, cornea and lacrimal ducts in the first place. Proton therapy is an emerging method and its progressive development, thanks to the implementation of new facilities, has allowed for its clinical application also for the treatment of CM, with mono-institutional cases limited to small patient populations.

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